VOLUME 63 *February 1951* NUMBER 2

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS

The Fluctuation of the Tuberculin Reaction in Different Geographic Areas and Its Relationship to Resistance. JOSEPH D. ARONSON 121

The Importance of the Tuberculin Test in the Differential Diagnosis of Pulmonary Lesions. C. EUGENE WOODRUFF AND W. LEONARD HOWARD 140

Endothelioma (Mesothelioma) of the Pleura. A Review with a Report of Seven Cases, Four of Which Were Extirpated Surgically. LEW A. HOCHBERG 150

Bronchogenic Carcinoma as a Differential Diagnostic Problem in Pulmonary Disease. I. Carcinoma Arising from Major Bronchi Uncomplicated by Secondary Infection. JOHN E. MOYER AND ALFRED J. ACKERMAN 176

Hemoptysis in Chest Clinic Patients. AARON D. CHAVES 194

A Clinical, Functional, and Needle Biopsy Study of the Liver in Pulmonary Tuberculosis. MARVIN SEIFE, BRUCE J. KESSLER, JOSEPH HOFFMAN, AND JAMES R. LISA 202

Ribs from Thoracoplasty as a Possible Source of Homogenous Bone Grafts. PAUL F. HAUSMANN 210

The Absorption of the Sodium Salt of Para-aminosalicylic Acid (PAS) from the rectum. CHARLES W. RIEBER, HERTA KUSCHINSKI, AND MAX M. FRIEDMAN 213

Case Reports:

Esophagobronchial Fistula Associated with Severe Hemorrhages. Treated by Surgical Excision and Lobectomy. HERBERT C. MAIER 220

Tuberculoma of the Cerebellopontine Angle Simulating Acoustic Neuroma. CHARLES W. ELKINS AND FRANK J. KACK 227

American Trudeau Society: Notes 230

Abstracts 21

ANNUAL MEETING—CINCINNATI, OHIO
May 15–18, 1951

See inside back cover

Published Monthly at Mount Royal and Guilford Avenues, Baltimore 2, Maryland by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 19, N. Y.

Copyright 1951 by the National Tuberculosis Association

PRINTED IN U. S. A.

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY

EDITOR-IN-CHIEF
ESMOND R. LONG
Philadelphia, Pa.

MANAGING EDITOR
WALSH McDERMOTT
New York, N. Y.

EDITORIAL BOARD

W. EDWARD CHAMBERLAIN, Philadelphia, Pa.
HALBERT L. DUNN, Washington, D. C.
H. CORWIN HINSHAW, San Francisco, Calif.
KIRBY S. HOWLETT, JR., Shelton, Conn.
JOHN C. JONES, Los Angeles, Calif.
ALEXANDER D. LANGMUIR, Atlanta, Ga.
JOHN D. STEELE, Milwaukee, Wis.
WILLIAM B. TUCKER, Minneapolis, Minn.
ARTHUR J. VORWALD, Trudeau, N. Y.

HELEN W. MILLER
Editorial Secretary

NOTICE TO SUBSCRIBERS AND CONTRIBUTORS

THE AMERICAN REVIEW OF TUBERCULOSIS is published by the National Tuberculosis Association and issued monthly about the first of the month. THE AMERICAN REVIEW OF TUBERCULOSIS is the official journal of the American Trudeau Society. A volume includes six numbers and begins with the January and July numbers.

Subscription: The subscription price of the REVIEW is $10 for the calendar year. Checks should be made payable to Collier Place, Treasurer.

Character of the Review: The REVIEW invites the submission of original manuscripts on any phase of tuberculosis, nontuberculous pulmonary diseases, and related subjects of interest.

MANUSCRIPTS

Contributors are requested to pay particular attention to the following rules governing the preparation of manuscripts. Failure to follow these rules is a frequent cause of delay in the publication of articles.

Manuscripts should be sent in duplicate to the office of the Managing Editor, Dr. Walsh McDermott, 1790 Broadway, New York 19, N. Y., mailed flat, and transmitted by first-class mail with postage for return if not acceptable. They should be in English, double-spaced, typewritten on one side of the page, with wide margins. Tabular data should not be included in the text but should be presented in separate tables with appropriate reference in the text. All case reports should be written in complete sentences. Authors should exercise particular care in the preparation, notation, and description of figures and tables. References should be in REVIEW style. Each table must be accompanied by a descriptive title, and a suitable legend must be provided for each figure. Drawings must be made with india ink and all lettering should be made with a stencil. The quality of the reproduction of a roentgenogram depends upon both the quality of the original picture and of the glossy print obtained from photographing that picture. If a contributor does not have facilities available, preparation of figures or reproduction of roentgenograms may be handled through the REVIEW office. Under those circumstances, the contributor should supply a neat, properly proportioned, and suitably entitled drawing or the original roentgenogram, and will be expected to defray the cost of these services.

The publishers will not be responsible for manuscripts, illustrations, etc., lost in transit. In order to save expense for authors' corrections in proof, manuscript should be carefully revised by the author before submission.

Abstracts: Authors wishing to have abstracts of their papers appear in ABSTRACTS OF TUBERCULOSIS will facilitate their publication by sending concise abstracts or reprints to the Managing Editor.

Reprints: Fifty reprints without covers of articles will be furnished to authors free of charge when requested in advance. A table showing cost of additional reprints with an order blank is submitted with proofs to the authors.

Single Copies: The price of single copies of this number of THE AMERICAN REVIEW OF TUBERCULOSIS is one dollar postpaid.

Advertising: Rates will be furnished by THE AMERICAN REVIEW OF TUBERCULOSIS, 1790 Broadway, New York 19, N. Y., on request.

The Publishers reserve the right to decline any advertising submitted and to censor all copy. Acceptance of an advertisement does not constitute official endorsement of the product advertised.

Entered as second-class matter March 9, 1917, at the post office at Baltimore, Md., under the Act of August 24, 1912. Acceptance for mailing at special rate of postage provided for in section 1103, Act of October 3, 1917. Authorized on July 2, 1918.

3 IMPORTANT FORMS OF HEYDEN ORAL PENICILLIN

FINE HEYDEN CHEMICALS

Under your own label, you can now offer your customers 3 popular and highly effective ORAL forms of Heyden Penicillin, in a wide range of dosages to meet the exacting requirements of the medical and hospital fields.

SOLUBLE TABLETS: Crystalline Penicillin G Potassium (50,000 and 100,000 units, sealed in foil).

TROCHES: Crystalline Penicillin G Potassium (5,000 units, in silver foil; 10,000 units, in gold foil). Pleasantly flavored, slow to dissolve.

BUFFERED TABLETS: Crystalline Penicillin G Potassium (50,000, 100,000 and 250,000 units sealed in foil).

Remember!—when you standardize on Heyden antibiotics, both you and your trade are assured of superior quality, uniformity and potency—regardless of the form, dosages or quantity you purchase.

Other Heyden Penicillin and Streptomycin Products

PENICILLIN

Vials: Crystalline Penicillin G Potassium or Sodium; Crystalline Procaine Penicillin G in Sesame Oil with 2% Aluminum Monostearate w/v (cartridges, single- and multiple-dose vials) (also available in fortified form).

STREPTOMYCIN

Vials: Crystalline Dihydrostreptomycin Sulfate (1-gm. and 5-gm.).

Dihydrostreptomycin Sulfate (1-gm. and 5-gm.).

Streptomycin Sulfate (1-gm. and 5-gm.).

MANUFACTURER-DISTRIBUTORS

will be interested in Heyden's bulk service to packagers of penicillin and streptomycin. Cartons, unit containers, technical literature and package inserts, are available for your OWN personalized service. Write today for detailed particulars.

HEYDEN CHEMICAL CORPORATION

MEAT...and the PROTEIN NEEDS of the DIABETIC

Not less but *more protein* than the traditional gram per kilo of body weight recommended for the non-diabetic individual promotes an increased sense of well-being in the diabetic patient. Liberal amounts of biologically excellent protein, such as that provided by *meat,* are therefore especially useful in dietotherapy.

For supporting the well-being and vigor of the patient, increasing his resistance to infection, and minimizing many of the degenerative changes common in diabetes mellitus, maintenance of body protein reserves is particularly important.[1,2] The former belief that protein foods, especially meat, engender hypertension and arteriosclerosis, is no longer tenable. On the contrary, deficits in dietary protein are apt to initiate anemia, hypoproteinemia, and retrogressive processes in the kidneys and other organs or tissues.

Ample amounts of high-quality protein foods in the prescribed diet—including generous amounts of meat—are important for maintaining a good nutritional state in the diabetic patient. Such a diet provides the nutritional essentials required in overcoming infections and in prompter healing of traumatic wounds.

Meat, however, is valuable to the patient for more than just its biologically excellent protein. It also furnishes important amounts of iron, thiamine, riboflavin and niacin, and of the newly discovered vitamin B_{12} which, among its several functions, promotes efficient utilization of protein.

(1) Mosenthal, H. O.: Management of Diabetes Mellitus: An Analysis of Present-Day Methods of Treatment, Ann. Int. Med., 29:79 (July) 1948.

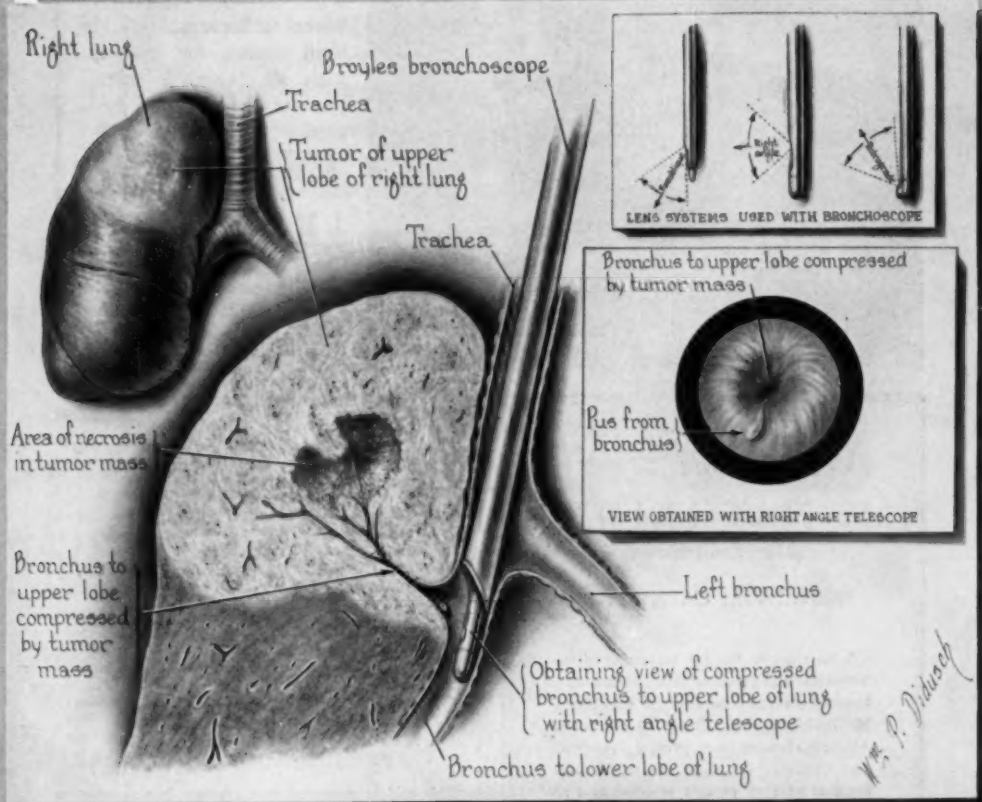
(2) McLester, J. S.: Nutrition and Diet in Health and Disease, 5th ed., Phil., W. B. Saunders Company, 1949, page 364.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago...Members Throughout the United States

THE *Broyles* BRONCHOSCOPE


Right lung
Broyles bronchoscope
Trachea
Tumor of upper lobe of right lung
Trachea
Area of necrosis in tumor mass
Bronchus to upper lobe compressed by tumor mass
Left bronchus
Obtaining view of compressed bronchus to upper lobe of lung with right angle telescope
Bronchus to lower lobe of lung
LENS SYSTEMS USED WITH BRONCHOSCOPE
Bronchus to upper lobe compressed by tumor mass
Pus from bronchus
VIEW OBTAINED WITH RIGHT ANGLE TELESCOPE

The illustration shows a case of suspected tumor of upper lobe of right lung in which x-ray findings were inconclusive. The Broyles Bronchoscope with right angle lens system disclosed a compressed bronchus, and a diagnosis of tumor was made.

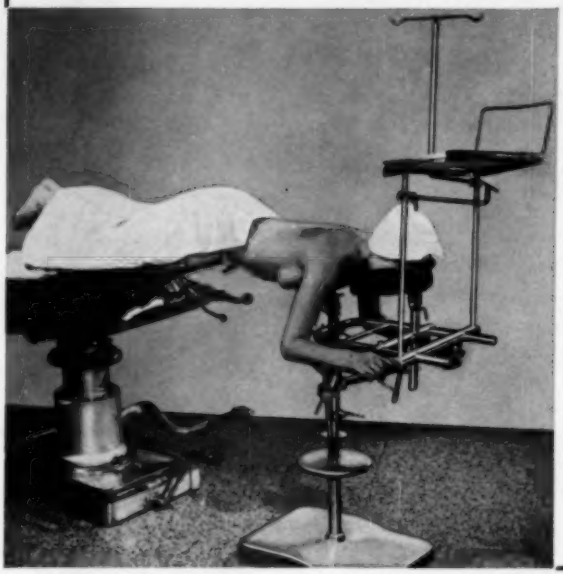
ESTABLISHED IN 1900 BY REINHOLD WAPPLER

FREDERICK J. WALLACE, *President*

American Cystoscope Makers, Inc.

1241 LAFAYETTE AVENUE NEW YORK 59, N. Y.

The NACLERIO SUPPORT *for* Prone-Position Surgery



used in conjunction with any standard operating table, to keep maximum vital capacity, minimize mediastinal shift, prevent contralateral spillage, and provide ideal access for surgery, with all favorable variations of the patient's position.

SIMPLE—INEXPENSIVE—PORTABLE—VERSATILE

Write for Circular

J. H. EMERSON CO.

22 COTTAGE PARK AVENUE
CAMBRIDGE 40, MASSACHUSETTS

Makers of
EMERSON
LUNG IMMOBILIZERS

Maryknoll
SANATORIUM
(Maryknoll Sisters)

MONROVIA, CALIFORNIA

• A Sanatorium for the treatment of tuberculosis and other diseases of the lungs. Located in the foothills of the Sierra Madre Mountains, Southern exposure. Accommodations are private, modern, and comfortable. Rates are moderate. General care of patient is conducive to physical and mental well being.

SISTER MARY PIETA
Superintendent

E. W. HAYES, M.D.
Medical Director

NURSING IN PREVENTION AND CONTROL OF TUBERCULOSIS

By H. W. HETHERINGTON, M.D., M.R.C.P. (London)

Chief of Clinic of the Henry Phipps Institute, University of Pennsylvania

and FANNIE W. ESHLEMAN, R.N., B.S.

Supervisor of Public Health Nursing of the Henry Phipps Institute, University of Pennsylvania

THIRD REVISED EDITION

This widely accepted text appears in a completely revised and reset form. It contains the latest available data on morbidity and mortality from tuberculosis, laboratory examinations, detection of case finding, consideration of antibiotic treatment, surgical treatment, rehabilitation, and compulsory isolation of infectious patients. Special attention is given to the *nursing care* of the patient, including the sociological and psychological aspects. $4.50

G. P. PUTNAM'S SONS

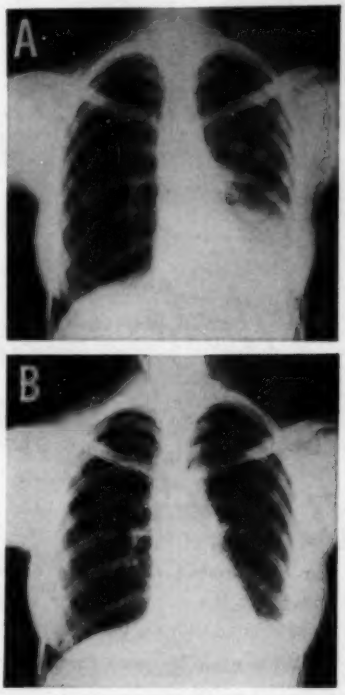
2 West 45th Street New York 19, N. Y.

Effective Chemotherapy in TUBERCULOSIS

DIHYDROSTREPTOMYCIN or Streptomycin, used alone or in combination with para-aminosalicylic acid, is recognized as a valuable and, in some instances, an essential adjuvant in the treatment of selected types and stages of tuberculosis.

Para-aminosalicylic acid is capable of inhibiting or significantly delaying the emergence of bacterial resistance to dihydrostreptomycin or streptomycin.

These drugs are not to be regarded as substitutes for traditional therapeutic methods. Rather, they serve best when properly integrated with bed rest and, where necessary, collapse measures or other forms of surgery.



A. Before Treatment
(9 days prior to Dihydrostreptomycin therapy) Diffuse lobular tuberculous pneumonia, lower half of left lung; thin-walled cavity above hilus (3 x 3.5 cm.).

B. After 3 Months' Treatment
(2 days after discontinuance of Dihydrostreptomycin) Considerable clearing of acute exudative process in the diseased lung; cavity smaller and wall thinner.

Detailed literature on the subject of chemotherapy in tuberculosis will be supplied upon request.

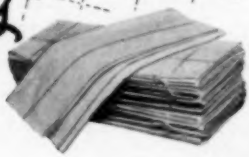
COUNCIL ACCEPTED

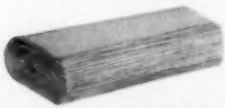
MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

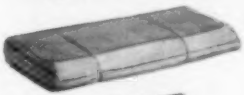
Merck Antituberculosis Agents

Streptomycin Calcium Chloride Complex Merck	Para-Aminosalicylic Acid Merck (PAS)	Crystalline Dihydrostreptomycin Sulfate Merck

"That's when we began using White Knight Linens"







The chart above reflects the experience of many hospitals throughout the country. Better service and reduced costs go hand in hand with the use of White Knight Linens.

What could be more natural? Real costs are always determined by grade and length of service. And White Knight Linens are notable for both *good* service and *long* service.

Again, what could be more natural? For White Knight Linens are specially selected for hospital use. Blankets, sheets, bed spreads, towels and toweling, yard goods, table linens — all must *prove* their worth before given the White Knight Label.

If you are not already using White Knight Linens make it a point to test some against your present supplies. Remember that White Knight Linens, like every other item in the Will Ross, Inc. line are *Unconditionally Guaranteed.*

White Knight

White Knight Linens are sold only by Will Ross, Inc.

WILL ROSS, INC.

Manufacturers and Distributors of Hospital and Sanatorium Equipment and Supplies

Milwaukee 12, Wisconsin

THE AMERICAN REVIEW
OF
TUBERCULOSIS

VOLUME 63 | *February 1951* | NUMBER 2

THE FLUCTUATION OF THE TUBERCULIN REACTION IN DIFFERENT GEOGRAPHIC AREAS AND ITS RELATIONSHIP TO RESISTANCE[1]

JOSEPH D. ARONSON

(Received for publication October 26, 1950)

INTRODUCTION AND REVIEW OF LITERATURE

The observations of different investigators indicate that the tuberculin reaction may persist, fluctuate, fade temporarily, or disappear. A transitory decrease or disappearance of the tuberculin reaction has been observed in measles (1–6), scarlet fever (3, 4), secondary syphilis (7, 8), pertussis (9), influenza (10, 3), diphtheria (3), far advanced tuberculosis, tuberculous meningitis (11, 12), sarcoidosis (13, 14), pregnancy (15–18), leukemia (19), cirrhosis of the liver, and icterus (19). The disappearance of the tuberculin reaction following frequently repeated small doses of tuberculin has long been recognized. It has also been reported that the tuberculin reaction may be modified by, or disappear after, collapse therapy (20, 21), following general anesthesia (22), and in the course of small pox vaccination (23). Gernez (24) has observed a more intense tuberculin reaction on the paralyzed side of hemiplegics than on the unaffected side. The tuberculin reaction may be modified in tuberculous guinea pigs by thyroidectomy (25) or by feeding a vitamin C-free diet (26, 27, 28). Willis (29) has shown that the waning and disappearance of the tuberculin reaction parallels the retrogression of the tuberculous process in guinea pigs infected with the avirulent R_1 strain of tubercle bacillus.

The tuberculin reaction may disappear in animals which have a natural resistance to certain types of tubercle bacilli. Thus, cattle infected with human-type tubercle bacilli gradually lose their sensitivity to tuberculin (30). Similarly, Elder and Lee (31) have found that cattle exposed to tuberculous chickens react to the tuberculin prepared from avian tubercle bacilli. When these cattle are removed for two to five months from their source of infection, the tuberculin reaction decreases and finally disappears, only to reappear when they are re-exposed to avian infection.

The effect of antihistaminic drugs on the tuberculin reaction has been investigated. Boquet (32) and Friedman and Silverman (33) found that antihistaminic

[1] From The Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania; and the Health Division, Office of Indian Affairs, Department of the Interior, Washington, D. C.

drugs did not inhibit the tuberculin reaction, and Crief, Levine, and Aaron (34) noted that neither antihistaminic drugs nor rutin interfered with the development of the tuberculin reaction. Weiser, Evans, and St. Vincent (35) were unable to protect tuberculous guinea pigs against systemic tuberculin shock by the administration of an antihistaminic drug. On the other hand, Sarber (36) and Graub and Barrist (37) claim that cutaneous hypersensitivity to tuberculin was depressed or abolished by these drugs.

The action of adrenocorticotrophic hormone and of cortisone on diseases of allergic nature led to studies on the effect of these agents on the bacterial type of hypersensitivity. Harris and Harris (38) noted that after treatment with cortisone tuberculous animals no longer reacted to tuberculin. Cutaneous hypersensitivity to tuberculin reappeared in three to six days after cortisone was discontinued. They also found that fatal tuberculin shock and hemorrhage of the adrenal could be prevented in tuberculous guinea pigs when these animals were first treated with cortisone. Long and Favour (39) found that the administration in man of either adrenocorticotrophic hormone or cortisone resulted in alteration or obliteration of the tuberculin reaction. These changes in the tuberculin reaction were temporary in nature, and hypersensitivity to tuberculin reappeared seven to twenty-eight days after treatment was discontinued. In many instances a lighting up of the tuberculin reaction was noted thirty-six hours after the cessation of treatment. The alteration of the tuberculin reaction bore no relationship to changes in the serum globulin, sedimentation rate, or the intradermal reaction to histamine. Carlisle, Gibson, and Schmatolla (40) noted, in guinea pigs immunized with heat-killed tubercle bacilli, that treatment with cortisone not only inhibited the tuberculin reaction but also inhibited the development of a Koch phenomenon in these animals.

It is possible that the decrease in intensity or disappearance of the tuberculin reaction in the course of certain diseases may be transitory because of changes in the reactivity of the cutaneous capillaries rather than desensitization. Pilcher (41) observed a close parallel between the reaction of the skin to the intracutaneous injection of codeine and to tuberculin. The reaction to codeine and to tuberculin decreased or disappeared during the course of measles or tuberculous meningitis. Brahic and Veyron (42) found a definite correlation between the intracutaneous reaction to Old Tuberculin and to histamine. The present writer has observed a delayed or atypical reaction to the transcutaneous application of histamine in patients suffering from far advanced pulmonary tuberculosis and who had failed to react to 1.0 mg. of OT.

Howe (43) has presented evidence which he believes indicates that the cutaneous reactivity to OT may be modified by meteorologic conditions. The observations of Ossoinig (44) over a three-year period indicate that sensitivity to tuberculin is lowest during the summer months. The writer has also observed for a number of years that the reaction of tuberculous guinea pigs to tuberculin is less marked and more irregular during the summer months. Whether or not this decreased sensitivity may be due to dehydration rather than to meteorologic conditions has not been investigated.

That the ability to react to tuberculin may disappear in man has been recog-

nized for many years. Austrian (45) observed that 10 of 133 children who initially gave a positive Pirquet reaction failed to react five years later. Lloyd and MacPherson (46) reported that the tuberculin reaction had disappeared in 4 per cent of 700 persons who reacted to tuberculin eighteen to twenty-four months previously. Dahlstrom (47) found among 2,490 persons who reacted, at least once, to the intracutaneous administration of tuberculin that 2,130, or 85.5 per cent, reacted to either 0.01 mg. of OT or to 0.00002 mg. of PPD. Of this group, 2.8 per cent failed to react to larger amounts of tuberculin when tested subsequently. On the other hand, of the 360 persons, or 14.5 per cent, of the original group who reacted only to the larger dose of either 0.1 mg. or 1.0 mg. of OT or to 0.005 mg. of PPD, 76.7 per cent subsequently became negative. In this study, loss of the tuberculin reaction occurred more frequently among those with a low level of tuberculin sensitivity, in members of those households where the least possible exposure to tuberculosis existed, among those of Italian origin, and in those less than 15 years of age. Zacks and Sartwell (48) retested after ten years 1,023 inmates of a mental institution who had been tested previously with 0.01 and 1.0 mg. of OT. Using the same technique and dosage of tuberculin, it was found that 3.2 per cent had reverted from positive to negative and that, of the 131 persons who had failed to react to tuberculin in the original examinations, 55 per cent had become positive during the intervening ten years. As in Dahlstrom's series, the reversions were more frequent among those less than fifteen years of age.

Dr. Camille Kereszturi Cayley (49) noted that, of 258 persons who reacted to 0.01 or 0.1 mg. of OT, 21, or 8.1 per cent, failed to react to OT when retested from six months to ten years later.

While the disappearance of the tuberculin reaction is relatively infrequent in those infected with viable, virulent tubercle bacilli who have developed a high degree of tuberculin sensitivity, it occurs more frequently and more rapidly among those immunized with the avirulent BCG culture. Kereszturi, Rosenberg, and Park (50) found that the tuberculin reaction began to fade and disappear as early as six months after the administration of BCG vaccine.

In order to study the stability and persistence of the tuberculin reaction, one needs to follow a group of persons over a long period of time and at regular intervals, using preferably the same lot of tuberculin or tuberculin of comparable potency. The dilution, administration of the tuberculin, and the interpretation of the reactions should be carried out under comparable conditions and preferably by the same personnel. Such an opportunity offered itself when the Office of Indian Affairs of the United States Department of the Interior and The Henry Phipps Institute, University of Pennsylvania, undertook a study of the value of BCG vaccine in the control of tuberculosis among some Indians of the United States and Alaska.

PLAN OF INVESTIGATION

In 1935–1937 a group of 3,025 Indians, ranging in age from less than one year to twenty years, failed to react to the intracutaneous injection of both 0.00002 and 0.005 mg. of tuberculin PPD. Fifteen hundred and sixty-five of these per-

sons received BCG vaccine intracutaneously, while 1,460, who served as controls,[2] received sterile physiologic salt solution. These 3,025 Indians lived in five different geographic areas of the United States and Alaska: Pima Indians, on the Pima Agency, Arizona; Arapaho and the Shoshone tribes, on the Wind River Agency, Wyoming; Rosebud Sioux, on the Rosebud Agency, South Dakota; Chippewas, on the Turtle Mountain Agency, North Dakota; and Tlingits, Haida, and Tsimshian Indians, in twelve villages of southeastern Alaska. These persons were followed annually for nine to eleven years by means of the tuberculin test and roentgenographic examination of the chest (51, 52).

Materials and Methods

From the inception of this study in 1935 to 1941, the PPD used for the tuberculin test was prepared by precipitating the tuberculoprotein with trichloracetic acid (53). From 1941 to 1946, when the study was terminated, PPD-S, prepared by precipitating the tuberculoprotein with ammonium sulfate (54), was used. Both preparations of PPD were prepared by Dr. Florence Seibert, Henry Phipps Institute, to whom we acknowledge our indebtedness. Throughout the entire course of this study, fresh dilutions were prepared daily in sterile physiologic saline from the concentrated solution of tuberculin PPD or PPD-S. With but few exceptions, the tuberculin injections and interpretations were made by Miss Erma Parr, R. N., who was especially trained for this purpose, or by the writer.

An initial injection of 0.00002 mg. of PPD in a total volume of 0.1 cc. was made in the skin over the volar surface. If, after forty-eight hours there was no local inflammatory reaction, or if the reaction was slight or doubtful, a second injection of 0.005 mg. of PPD was made and the results interpreted forty-eight hours later. The local reaction was described objectively by measuring and recording the largest axes of edema and by estimating and recording the thickness of the edematous skin. In addition, note was made of the occurrence of intense redness or discoloration, petechial hemorrhage, ecchymosis, vesiculation, necrosis, lymphangitis, subjective symptoms, if any, and any other unusual reaction. The results were arbitrarily graded according to a classification previously outlined (55). Redness was found to be so variable both in duration and extent and so easily modified by many factors that no routine record was made of the redness usually associated with edema. When redness alone was present, however, or when it was associated with slight edema, a notation was made.

OBSERVATIONS

With increasing observations extending over a period of nine to eleven years, it became evident that fluctuations and reversions of the tuberculin reaction from positive to negative occurred most frequently among the Indians of the Pima Agency, Arizona.

The percentage of those tested with tuberculin each year during the course of this study varied from 96.8 to 72.1 among the controls and from 96.4 to 68.6 among the BCG-vaccinated group. Obviously, not all cases were tested every year of the study, and the small number lost after one or two years of observation have been excluded from this analysis. During World War II there was a period of two years when field studies had to be temporarily discontinued.

[2] In the subsequent discussion the terms "control" or "controls" are used, in the interest of brevity, to designate an unvaccinated person or persons.

Pattern of Tuberculin Reaction

The patterns of the tuberculin reactions observed in these persons over the period of this study are so diverse that they have been grouped arbitrarily under the following 10 categories:

1. *Consistently negative:* Those who failed at all times to react to the intracutaneous injection of both 0.00002 mg. and 0.005 mg. of PPD or PPD-S tuberculin.

2. *Fluctuation between negative and doubtful:* Those who either failed to react to both doses of tuberculin or who gave a doubtful or atypical reaction to 0.005 mg. of tuberculin, but at no time gave a definite reaction to either dose of tuberculin. A definite increase in this pattern occurred when PPD-S, the ammonium sulfate preparation of tuberculoprotein, replaced the original PPD or trichloracetic acid tuberculoprotein.

3. *Consistently positive to 0.00002 mg. of tuberculin:* Those who developed a high level of tuberculin sensitivity and, once having become positive, consistently reacted to this small dose of tuberculin.

4. *Consistently positive to 0.005 mg. of tuberculin:* Those with a low level of tuberculin sensitivity who once having reacted to 0.005 mg. of tuberculin were consistently positive to this dose only.

5. *Decreasing sensitivity:* Those who reacted originally to 0.00002 mg. of tuberculin but who subsequently reacted to 0.005 mg. of tuberculin only.

6. *Increasing sensitivity:* Those who reacted at first only to 0.005 mg. of tuberculin and who subsequently reacted to 0.00002 mg. of tuberculin. This increased sensitivity in the case of the BCG-vaccinated persons may be due to superimposed spontaneous infection with virulent tubercle bacilli.

7. *Fluctuating positive:* Those who showed a variation in the degree of tuberculin sensitivity. In this category are those who reacted to 0.005 mg. or 0.00002 mg. of tuberculin and who subsequently fluctuated in their degree of sensitivity to the two doses, but who at no time failed to react definitely to tuberculin.

8. *Fluctuating positive with negative or doubtful reactions:* Those who showed a variation in the degree of tuberculin sensitivity and who at some time gave a negative or doubtful reaction to 0.005 mg. of tuberculin, but who subsequently reacted to one or the other dose of tuberculin.

9. *Reversion to negative or doubtful from positive with 0.00002 mg.:* Those who reacted originally to 0.00002 mg. of tuberculin and who ultimately failed to react or who gave a doubtful reaction to 0.005 mg. of tuberculin. A number of persons became negative or doubtful during the last year of this study only.

10. *Reversion to negative or doubtful from positive with 0.005 mg.:* Those who reacted to 0.005 mg. of tuberculin and who subsequently either failed to react or who gave a doubtful reaction to this dose of tuberculin. A certain number showing this pattern were negative or doubtful for the last year of observation only.

The tuberculin reaction for the control, unvaccinated, and the BCG-vaccinated groups is presented according to patterns of reaction to tuberculin and by agency in table 1.

Unvaccinated group: Among the unvaccinated group the percentage of those who failed consistently to react to 0.005 mg. of tuberculin and the percentage who developed a persistent reaction to 0.00002 mg. of tuberculin, indicating a high level of tuberculin sensitivity, varied within wide limits among the Indians of the different agencies, and in the case of the Wind River Agency among the

TABLE 1

Patterns of PPD Tuberculin Reactions among Unvaccinated and BCG-vaccinated Groups in Different Areas

Controls

AGENCY	ORIGINAL NUMBER	NUMBER RETESTED	YEARS OBSERVED	CATEGORIES																			
				1 Consistently Negative		2 Fluctuating Negative or Doubtful		3 Consistently Positive to 0.00002 mg.		4 Consistently Positive to 0.005 mg.		5 Decreasing Sensitivity 0.00002 mg. to 0.005 mg.		6 Increasing Sensitivity 0.005 mg. to 0.00002 mg.		7 Fluctuating Positive		8 Fluctuating Positive with Negative or Doubtful		9 Reversion from 0.00002 mg. to Negative or Doubtful		10 Reversion from 0.005 mg. to Negative or Doubtful	
				Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Pima A, Arizona	263	260	11	57	21.9	40	15.5	29	11.3	13	5.0	1	0.4	4	1.3	34	13.1	20	7.7	2	0.8	60	23.0
* Shoshone	85	83	11	42	50.6	16	19.3	16	19.3	2	2.4	0	—	0	—	2	2.4	1	1.2	4	4.8		
* Arapaho	106	99	11	14	14.2	15	15.2	51	51.6	2	2.0	0	—	7	7.1	1	1.0	5	5.1	0	—	4	3.8
Turtle Mt., N. D.	162	160	11	51	31.9	32	20.1	53	33.6	7	4.4	1	0.6	4	2.5	7	4.4	1	0.6	1	0.6	4	2.5
Pima B, Arizona	87	87	10	22	25.3	15	17.2	12	13.9	7	8.1	1	1.1	2	2.3	0	0.2	5	5.7	0	—	15	17.3
Rosebud, S. D.	291	286	9	69	24.1	50	17.5	120	41.9	10	3.5	3	1.1	16	5.5	1	0.3	3	1.1	0	—	14	5.0
Alaska	486	457	9	134	29.4	58	12.7	217	47.5	8	1.7	1	0.3	21	4.6	0	—	4	0.9	3	0.6	11	2.4
Total	1,460	1,432		389	27.2	226	15.8	497	34.7	49	3.4	7	0.5	54	3.8	51	3.6	40	2.8	7	0.4	112	7.8

BCG-Vaccinated

AGENCY	ORIGINAL NUMBER	NUMBER RETESTED	YEARS OBSERVED	CATEGORIES																			
				1 Consistently Negative		2 Fluctuating Negative or Doubtful		3 Consistently Positive to 0.00002 mg.		4 Consistently Positive to 0.005 mg.		5 Decreasing Sensitivity 0.00002 mg. to 0.005 mg.		6 Increasing Sensitivity 0.005 mg. to 0.00002 mg.		7 Fluctuating Positive		8 Fluctuating Positive with Negative or Doubtful		9 Reversion from 0.00002 mg. to Negative or Doubtful		10 Reversion from 0.005 mg. to Negative or Doubtful	
				Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Pima A, Arizona	288	283	11	1	0.4	2	0.8	18	7.1	9	3.5	17	6.7	11	4.3	115	45.5	52	20.6	12	4.8	16	6.3
* Shoshone	110	106	11	0	—	0	—	22	20.8	11	10.4	4	3.8	15	14.1	46	43.4	5	4.7	0	—	3	2.8
* Arapaho	118	118	11	0	—	0	—	17	14.5	7	5.9	4	3.4	39	33.1	44	37.3	5	4.2	1	0.8	1	0.8
Turtle Mt, N. D.	170	167	11	0	—	0	—	28	16.8	11	6.5	7	4.2	31	18.6	67	40.1	14	8.4	1	0.6	8	4.8
Pima B, Arizona	97	97	10	0	—	1	1.0	4	4.1	9	9.3	2	2.0	19	19.7	35	36.1	15	15.5	1	1.0	11	11.3
Rosebud, S. D.	301	297	9	6	2.0	18	6.0	58	19.5	43	14.5	4	1.4	73	24.6	33	11.1	20	9.2	0	—	33	11.1
Alaska	511	505	9	0	—	0	—	146	29.1	14	2.8	8	1.5	214	42.6	104	20.7	6	1.2	3	0.6	8	1.5
Total	1,565	1,541		7	0.4	21	1.3	293	19.2	104	6.8	46	2.9	402	26.1	444	28.8	126	8.2	18	1.1	80	5.2

* Wind River Agency, Wyoming.

two different tribes living on the same agency. These variations reflect the differences in the incidence of tuberculous infection in these areas. Considerably less variation was observed among those who fluctuated between negative or doubtful reactions or who consistently gave a doubtful or atypical reaction. Many, if not all, reactions of this type may be nonspecific in character.

Consistent reactions to the larger dose of 0.005 mg. of tuberculin varied widely in the different agencies. They were most frequently observed among those living on the Pima and the Turtle Mountain agencies.

The persistence of the tuberculin reaction in those who first developed a high level of tuberculin sensitivity is in conformity with the observation of other investigators. In the present study it was found that only 0.5 per cent of those who originally reacted to 0.00002 mg. of tuberculin decreased in tuberculin sensitivity during the nine and eleven years of observation, while 0.4 per cent of this group subsequently failed to react to 0.005 mg. of tuberculin. In contrast, among those who originally developed a low level of tuberculin sensitivity, as indicated by reacting only to 0.005 mg. tuberculin, 7.8 per cent reverted to negative.

Increase of tuberculin sensitivity among the BCG-vaccinated was observed most frequently among those living on the Rosebud Agency, South Dakota, in Alaska, and among the Arapaho tribe of the Wind River Agency. Similarly a high level of tuberculin sensitivity was observed among the controls living in these two areas and among the Arapaho tribe.

On the Pima Agency, Arizona, fluctuations between a high level of tuberculin sensitivity and a low level were more marked, both among the vaccinated and the controls, than among those living on other agencies. Such fluctuations were least marked among the Indians of the Rosebud Agency, South Dakota, and Alaska. These findings are emphasized by the fact that the two different groups included from the Pima Agency show comparable results. Group "Pima A" initiated this study in 1936 and was under observation for eleven years; while "Pima B" represents a supplementary group not tested in 1936 but which was included in 1937 and was followed for ten years. Similarly fluctuating positive reactions reverting at times to negative or doubtful reactions to 0.005 mg. of tuberculin are higher among those living on the Pima Agency and among the Arapaho tribe.

BCG-vaccinated group: Evaluation of the positive reactions to tuberculin among the BCG-vaccinated group is complicated by several factors. First, the frequency and persistence of post-vaccinal tuberculin reactions varied with different lots of vaccine; and, second, variations in the incidence of superimposed tuberculous infection in the different areas modified the tuberculin reaction. A possible third factor may be geographical, as indicated by the marked fluctuations of the tuberculin reaction among the Pima Indians of Arizona.

The data presented in table 1 indicate that the parenteral administration of BCG vaccine induces a post-vaccinal tuberculin reaction in a high percentage of persons. Of those receiving BCG vaccine, only 0.4 per cent failed to react to both doses of tuberculin and 1.3 per cent fluctuated between negative and doubt-

ful reactions. The highest percentage of negative or doubtful reactions following vaccination was observed on the Rosebud Agency, where two lots of BCG vaccine prepared from slowly growing, dry colonies were used.

The level of tuberculin sensitivity is conspicuously lower after BCG vaccination than among the controls who have undergone a spontaneous infection with virulent tubercle bacilli. It will be noted from table 1 that, while among the vaccinated group 19.2 per cent reacted consistently to the smaller dose of tuberculin, 34.7 per cent of the control group followed this pattern of reaction. Furthermore, the percentage who developed a low level of tuberculin sensitivity and reacted to 0.005 mg. only was higher among the vaccinated than among the control group. Among the BCG-vaccinated, the high level of tuberculin sensitivity varied to a greater degree than among the controls. On the other hand, the percentage who showed an increase in sensitivity to tuberculin was conspicuously higher among the vaccinated than among the controls. This increase in tuberculin sensitivity in all probability is due to a superimposed tuberculous infection with virulent tubercle bacilli. Proof of this fact is that the increase in level of tuberculin sensitivity occurs most frequently among the Indians of the Rosebud Agency and southeastern Alaska and among the Arapaho tribe of the Wind River Agency, where the controls show a high incidence of consistent positive reactions to 0.00002 mg. of tuberculin, reflecting a high rate of tuberculous infection.

The variations in the stability of the tuberculin reactions are brought out more definitely when a simpler grouping is made. For this purpose both controls and vaccinated persons have been consolidated under three main headings: those who at no time gave a definite positive reaction; those who always reacted to one or the other dose of tuberculin; and those who reacted to one or the other dose of tuberculin, but subsequently reverted to negative or gave a doubtful reaction either temporarily or for the period of this study. This classification is presented graphically in figure 1.

It is evident (figure 1) that the incidence of tuberculous infection developing among the control group after the initiation of the study, as indicated by the percentage of positive reactors to tuberculin, differs widely in the areas studied, while among the BCG-vaccinated group the incidence of positive reactions is more uniform. On the other hand, the reversion rate, both among the controls and the BCG-vaccinated groups "A" and "B" of the Pima Agency, is conspicuously higher. The high percentage of reversions noted among the Indians of the Rosebud Agency is undoubtedly due to the use of two lots of BCG vaccine with low antigenicity.

Antigenicity of different preparations of BCG vaccine: Among those of the BCG-vaccinated group who were observed for nine to eleven years following vaccination, the possibility existed that variations in the patterns of the tuberculin reaction may have been due to variations in the antigenicity of different preparations of BCG vaccine. Aronson, Parr, and Saylor (56) found that the percentage of vaccinated persons who reacted one and two years after vaccination to tuberculin, as well as the level of tuberculin sensitivity, varied with

different lots of vaccine. To evaluate the role of the antigenicity of the different preparations of BCG vaccine, the patterns of the tuberculin reaction, after nine to eleven years of observation, are correlated with the 13 different preparations of BCG vaccine used in this study and with the percentage and level of tuberculin sensitivity observed one year after vaccination. This and other pertinent data dealing with each lot of vaccine are presented in table 2.

A total of 1,481, or 94.7 per cent, of the 1,565 persons who received the BCG vaccine were retested one year later. Those vaccinated with lots 1 to 7 or 11 to 13, inclusive, reacted one year later to tuberculin in 92.6 to 100.0 per cent of

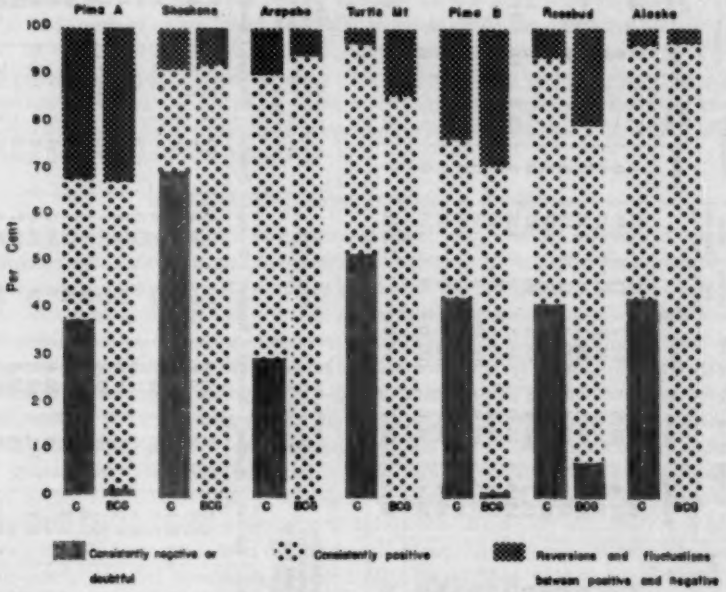


FIG. 1. Pattern of tuberculin reactions in different areas

cases. On the other hand, of those vaccinated with lots 8 and 9 only, 61.8 and 81.1 per cent, respectively, reacted to tuberculin. These two lots of vaccine were prepared from slowly growing, dry colonies.

It will be noted that after nine years of observation the highest percentage of consistently negative or fluctuating negative-to-doubtful reactions, or the reverse, occurred among those who received lots 8 and 9 vaccine.

Among those who received the different lots of BCG vaccine, during the nine to eleven years of observation a marked variation was noted in the percentage who developed a post-vaccinal high level of tuberculin sensitivity, or who showed an increased sensitivity from 0.005 mg. to 0.00002 mg. of PPD. These patterns of tuberculin reactions bore no direct relationship to the incidence or

TABLE 2

Patterns of PPD Tuberculin Reactions following Different Lots of BCG Vaccine

BCG VACCINE LOT NUMBER	AGENCY	ORIGINAL NUMBER VACCINATED	PER CENT TUBERCULIN POSITIVE ONE YEAR AFTER VACCINATION			YEARS OBSERVED	NUMBER RETESTED	CONSISTENTLY NEGATIVE		FLUCTUATING NEGATIVE OR DOUBTFUL		CONSISTENTLY POSITIVE TO 0.00002 MG.		CONSISTENTLY POSITIVE TO 0.005 MG.	
			To 0.00002	To 0.005	Total			Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1	Pima	88	48.2	44.4	92.6	11	85	1	1.2	2	2.4	7	8.2	2	2.4
2	Pima	169	61.4	33.3	94.7	11	168	0	—	0	—	11	6.6	7	4.2
3	*Wind River	101	59.3	36.3	95.6	11	97	0	—	0	—	22	22.7	11	11.3
4	*Wind River	115	39.6	59.5	99.1	11	115	0	—	0	—	15	13.1	7	6.1
5	*Wind River	12	33.3	66.7	100.0	11	12	0	—	0	—	2	16.6	0	—
6	Turtle Mt.	170	41.8	56.4	98.2	11	167	0	—	0	—	28	16.8	11	6.6
7	Pima	97	13.1	80.4	93.5	10	97	0	—	1	1.0	4	4.1	9	9.3
8	Rosebud	127	13.8	48.0	61.8	9	124	4	3.2	14	11.3	30	24.2	12	9.6
9	Rosebud	164	15.6	72.5	88.1	9	163	2	1.2	4	2.4	25	15.4	31	19.1
10	Rosebud	10	50.0	50.0	100.0	9	10	0	—	0	—	3	30.0	0	—
11	Alaska	268	37.8	61.0	98.8	9	262	0	—	0	—	72	27.5	8	3.1
12	Alaska	29	46.4	53.6	100.0	9	28	0	—	0	—	12	42.9	1	3.6
13	Alaska	215	35.4	64.6	100.0	9	213	0	—	0	—	62	29.2	5	2.3
Total		1,565	36.6	56.7	93.3		1,541	7	0.4	21	1.3	293	19.2	104	6.8

BCG VACCINE LOT NUMBER	AGENCY	DECREASING SENSITIVITY 0.00002 MG. TO 0.005 MG.		INCREASING SENSITIVITY 0.005 MG. TO 0.00002 MG.		FLUCTUATING POSITIVE		FLUCTUATING POSITIVE WITH NEGATIVE OR DOUBTFUL		REVERSION FROM POSITIVE TO 0.00002 MG. TO NEGATIVE OR DOUBTFUL TO 0.005 MG.		REVERSION FROM POSITIVE TO 0.005 MG. TO NEGATIVE OR DOUBTFUL	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1	Pima	4	4.7	5	5.9	32	37.6	19	22.3	7	8.2	6	7.1
2	Pima	13	7.7	6	3.6	83	49.4	33	19.6	5	2.9	10	5.9
3	*Wind River	3	3.1	11	11.3	43	44.4	4	4.1	0	—	3	3.1
4	*Wind River	4	3.5	38	33.0	43	37.4	6	5.3	1	0.8	1	0.8
5	*Wind River	1	8.3	5	41.8	4	33.0	0	—	0	—	0	—
6	Turtle Mt.	7	4.2	31	18.5	67	40.1	14	8.4	1	0.6	8	4.8
7	Pima	2	2.1	19	19.6	35	36.1	15	15.5	1	1.0	11	11.3
8	Rosebud	2	1.6	20	16.1	10	8.1	14	11.3	0	—	18	14.5
9	Rosebud	2	1.2	49	30.1	19	11.7	16	9.8	0	—	15	9.0
10	Rosebud	0	—	4	40.0	3	30.0	0	—	0	—	0	—
11	Alaska	4	1.5	115	43.9	51	19.4	4	1.5	3	1.2	5	1.9
12	Alaska	0	—	12	42.8	3	10.7	0	—	0	—	0	—
13	Alaska	4	1.9	87	40.8	50	23.5	2	1.0	0	—	3	1.3
Total		46	2.9	402	26.1	443	28.7	127	8.3	18	1.2	80	5.1

* Arapaho and Shoshone Tribes.

level of tuberculin sensitivity observed one year after vaccination. The high incidence and level of tuberculin reactions observed among the BCG-vaccinated group parallels that observed among the unvaccinated controls in the same areas.

A decrease in the tuberculin sensitivity from 0.00002 mg. to 0.005 mg. occurred most frequently in those areas which showed a low rate of tuberculous infection among the controls during the period of this study.

Fluctuation of the tuberculin reaction between high and low sensitivity, but associated at all times with a definite reaction to either dose of tuberculin, varied somewhat with the different lots of vaccine. It was most marked among those who had received either lots 8 or 9 BCG vaccine, while the number who received lot 10 vaccine was too small to be significant statistically. Instability of the tuberculin reaction, as indicated by fluctuation of the reaction between high and low level but associated at times with a definite negative or doubtful reaction, occurred most frequently among those who received lots 1, 2, and 7, all of whom lived on the Pima Agency.

Relationship of Hypersensitivity to Resistance

It is generally accepted that cutaneous sensitivity to tuberculin is evidence of a tuberculous infection and hence serves indirectly to indicate some degree of resistance to reinfection. It is on this basis that the antigenicity of BCG vaccine has been evaluated and loss of tuberculin sensitivity has served as an indication for revaccination. There is, however, much evidence which indicates that cutaneous hypersensitivity and resistance may occur independently of each other. Willis (29) immunized guinea pigs with the avirulent R_1 human strain of tubercle bacillus. With increasing time the tuberculin reaction decreased and finally disappeared. Despite the loss of sensitivity, the rate of development and extent of tuberculosis following infection with a virulent culture was conspicuously less in the immunized than in the control unvaccinated animals, and was unrelated to the cutaneous sensitivity to tuberculin. Rich (57) and Rich and McCordock (58) have presented evidence indicating that hypersensitivity does not necessarily parallel resistance. Duprez (59) found that repeated injections of BCG vaccine in guinea pigs induced resistance to infection with virulent tubercle bacilli despite the absence of allergy. Rothschild, Friedenwald, and Bernstein (60) abolished cutaneous hypersensitivity in tuberculous guinea pigs by repeated injections of increasing amounts of OT. Desensitization was maintained after the animals were infected with virulent tubercle bacilli by continuing the administration of OT. Not only did the desensitized immunized animals fail to react to tuberculin, but the intracutaneous injection of viable tubercle bacilli failed to elicit a Koch phenomenon. Despite the desensitization, the immunized animals resisted a challenge dose of virulent tubercle bacilli as well as, or better than, the non-desensitized immunized animals. Further evidence indicating the lack of correlation between hypersensitivity and resistance is that of Lewis and Loomis (61) who found that inbred guinea pigs with a low degree of resistance showed the highest degree of hypersensitivity. The present writer's observations

on the tuberculin reaction made over a period of many years in various parts of the United States and Alaska, covering different races, indicate that, while the incidence and the level of tuberculin sensitivity are high among Negroes and Indians, resistance to tuberculosis differs markedly. Among Negroes, rapidly progressing forms of this disease with rapid and extensive caseation, little fibrosis, and extensive involvement of the lymph nodes are frequently observed; while among the Indians tuberculosis is chronic in nature, usually associated with fibrosis and calcification, and comparable in nature with that observed among the white population.

DISCUSSION

Among the control and BCG-vaccinated groups living at the Pima Agency, Arizona, the tuberculin reaction was less stable than that observed among the controls and BCG-vaccinated persons of the other areas included in this study. Among the unvaccinated controls of this agency, the percentage of those whose tuberculin reaction fluctuated from one level of sensitivity to the other was higher than that observed in other areas, and reversions from positive to 0.005 mg. of PPD to negative or doubtful were conspicuously high. Among the BCG-vaccinated group, the percentage who showed a persistently high level of tuberculin sensitivity was lower than that observed among those living in the other areas. Fluctuations in the level of tuberculin sensitivity, interspersed at times with a negative or doubtful reaction, occurred frequently and reversions from positive to negative, while less frequent than those observed among the controls of the Pima Agency, were also higher among the BCG-vaccinated Pima Indians than in other areas.

The validity of these findings is strengthened by the fact that on the Pima Agency two distinct groups of both vaccinated and controls, separated by an interval of one year, were followed for ten to eleven years, respectively, and gave comparable results. The only other group comparable to that of the Pima Agency in the instability of the tuberculin reaction was that of the BCG-vaccinated persons living at the Rosebud Agency, South Dakota. In this instance, the instability of the tuberculin reaction is related to the use of two lots of BCG vaccine of low antigenicity, as indicated by the fact that one year after vaccination the tuberculin reaction was positive in only 61.8 and 88.1 per cent, respectively, of those who received these two lots of vaccine. Among those who received the eleven other lots of vaccine, approximately 95 per cent were positive one year later. On the other hand, the pattern of the tuberculin reaction among the control group living at the Rosebud Agency was comparable to that observed among the controls of the other areas.

That the instability of the tuberculin reaction among the Pima Indians may be nonspecific in nature, induced by organisms having some common antigenic factor with the tubercle bacilli, has been considered. Hauduroy (62), in a recent summary of the literature dealing with the specificity of the tuberculin reaction, concludes that animals inoculated with certain acid-fast saprophytes react to tuberculins prepared from these organisms, as well as to tuberculin prepared from tubercle bacilli. Since acid-fast bacteria are widely distributed in the soil,

water, moss, swamps, and other places, and since there are not at this time any objective data which would indicate that acid-fast saprophytes are more or less frequently found on the Pima Agency than in other areas, it cannot be assumed that they play a role in the fluctuations of the tuberculin reaction in Arizona. Proof that the instability of the tuberculin reaction among these Indians is not due to infection with acid-fast saprophytes is indicated by the fact that the instability of the tuberculin reaction occurred as frequently among the BCG-vaccinated as among the controls.

Despite the fact that the incidence and level of the tuberculin reaction one year after vaccination was comparable to that observed in the other areas, except the Rosebud Agency, the tuberculin reaction among the Pima Indians fluctuated and disappeared with increasing time to a greater degree.

The possibility that an intercurrent disease might in some manner influence skin reactivity to tuberculin was considered. Aronson, Saylor, and Parr (63) found that 83.6 per cent of the Indians tested on the Pima Agency reacted to the intracutaneous injection of coccidioidin, while calcified pulmonary lesions were found in 14.5 per cent of those who failed to react to tuberculin but reacted to coccidioidin. To determine what influence coccidioidomycosis might have on the tuberculin reaction, guinea pigs were first infected with a culture of *Coccidioides immitis* by Dr. C. Emmons of the National Institutes of Health, Bethesda, Maryland, whose cooperation is gratefully acknowledged. These animals were subsequently infected with a virulent culture of human-type tubercle bacillus and three weeks after infection with tubercle bacilli they, as well as tuberculous control guinea pigs, were injected intracutaneously with varying amounts of tuberculin. The tuberculin reaction in the animals suffering from both coccidioidomycosis and tuberculosis was comparable to that observed in the tuberculous guinea pigs.

The instability of the tuberculin reaction and the low levels of tuberculin sensitivity may be due to climatic factors. Mayer (64) found a decrease in the intensity of the tuberculin reaction, both in man and in guinea pigs, following a short exposure of the skin to ultraviolet rays. Similarly, skin which had been tanned by sunlight showed a definite reduction in the intensity of the tuberculin reaction. Other observers (65, 66) have also found that local areas of skin exposed to ultraviolet light failed to react or showed a diminished sensitivity to tuberculin and that the difference in sensitivity was unrelated to the degree of pigmentation.

The dark-skinned Indians of the Pima Agency live approximately 40 miles southeast of Phoenix, Arizona. The climate is that of the typically arid southwest. The average sunshine over a period of twenty-five years has been 84.4 per cent, and the intensity of sunlight at 10 a.m. on a typical morning in March was approximately 15,000 foot candles. Temperatures from 100° to 115°F. are not uncommon from June to September, inclusive, and the average rainfall per year is approximately 7.5 inches. Dryness and scaliness of the skin of school-age children is common. The instability of the tuberculin reaction among the Pima Indians may be related to these climatic factors.

The decrease or loss of cutaneous hypersensitivity among those living at the

Pima Agency may not necessarily represent a real loss of hypersensitivity, but rather the fact that the reactivity of the skin, not only to tuberculin but to other agents, may have been modified by climatic factors.

SUMMARY

1. The tuberculin reaction was observed annually for a period of nine to eleven years in 1,432 unvaccinated controls and in 1,541 BCG-vaccinated Indians, all of whom had failed originally to react to both 0.00002 and 0.005 mg. of PPD.

2. The Indians lived at the Pima Agency, Arizona; Wind River Agency, Wyoming; Turtle Mountain Agency, North Dakota; Rosebud Agency, South Dakota; and in twelve communities in southeastern Alaska.

3. The patterns of the tuberculin reactions of the control and BCG-vaccinated groups were classified arbitrarily on the basis of the persistence, fluctuation, or reversion of the reaction into ten different categories.

4. After nine to eleven years of study, a greater percentage of the controls showed a persistent, high degree of tuberculin sensitivity than did the BCG-vaccinated.

5. Among those who showed a high level of tuberculin sensitivity, as indicated by reacting to 0.00002 mg. of PPD, a small percentage of the controls and a higher percentage of the vaccinated showed a decrease in the level of tuberculin sensitivity or a reversion to negative.

6. Increased tuberculin sensitivity from 0.005 to 0.00002 mg. of PPD occurred most frequently among the BCG-vaccinated and particularly in those areas where the incidence and level of the tuberculin reaction was high, a fact suggesting that the BCG-vaccinated persons had undergone superimposed infection with virulent tubercle bacilli.

7. Fluctuation of the tuberculin reaction, as well as reversions from positive to negative, occurred most frequently among the controls and BCG-vaccinated persons living at the Pima Agency, Arizona.

8. The instability of the tuberculin reaction noted among the BCG-vaccinated living at the Pima Agency, Arizona, cannot be attributed to the low antigenicity of the BCG vaccine, but is possibly related to climatic factors such as excessive sunlight.

9. No relationship was found between the instability of the tuberculin reaction and the mortality from tuberculosis among those living at the Pima Agency. Among the controls observed for 3,952 person years, 9 died from this disease, while among the BCG-vaccinated observed for 4,085 person years one died from tuberculosis. The last-named person showed a marked Koch phenomenon forty-eight hours after vaccination and died two months later.

SUMARIO

La Fluctuación de la Reacción a la Tuberculina en Diversas Zonas Geográficas y Relación de la Misma con la Resistencia

1. La reacción a la tuberculina fué observada anualmente durante un período de nueve a once años en 1,432 testigos no vacunados y en 1,541 indios vacunados

con BCG, ninguno de los cuales había reaccionado primitivamente ni a 0.00002 ni a 0.0005 mg. de PPD.

2. Los indios vivían en las siguientes Agencias: Pima, Arizona; Wind River, Wyóming; Turtle Mount, Dakota del Norte; y Rosebud, Dakota del Sur; y además en doce colectividades del sudeste de Alaska.

3. Los patrones de las reacciones a la tuberculina en los grupos de testigos y de vacunados con BCG fueron clasificados arbitrariamente en diez categorías distintas a base de la persistencia, fluctuación o viraje de la reacción.

4. Al cabo de nueve a once años de estudio, un porcentaje mayor de los testigos que de los vacunados con BCG reveló un tenor persistente y alto de sensibilidad a la tuberculina.

5. Entre los que mostraron un alto tenor de sensibilidad a la tuberculina, según indica su reacción a 0.00002 mg. de PPD, un porcentaje pequeño de los testigos y algo mayor de los vacunados reveló disminución del tenor de sensibilidad a la tuberculina o viraje a negatividad.

6. Aumento de sensibilidad a la tuberculina con 0.005 a 0.00002 mg. de PPD ocurrió más frecuentemente entre los vacunados con BCG que habían experimentado una infección sobrepuesta con bacilos tuberculosos virulentos.

7. Fluctuaciones de la reacción a la tuberculina, así como virajes de positiva a negativa, alcanzaron su mayor frecuencia entre los testigos y los vacunados con BCG que vivían en la Agencia Pima, en Arizona.

8. La inestabilidad de la reacción a la tuberculina notada entre los vacunados con BCG que vivían en la Agencia Pima, Arizona, no puede imputarse a la escasa antigenicidad de la vacuna BCG, pero se halla posiblemente enlazada con factores climatológicos, tales como la excesiva luz solar.

9. No se observó la menor relación entre la inestabilidad de la reacción a la tuberculina y la mortalidad tuberculosa entre los que vivían en la Agencia Pima. Entre los testigos observados durante 3,952 persona-años, 9 murieron de la enfermedad, mientras que entre los vacunados con BCG observados durante 4,085 persona-años, uno murió de tuberculosis. Este último reveló un pronunciado fenómeno de Koch a las cuarenta y ocho horas de la vacunación y murió dos meses después.

RESUME

Fluctuations de la réaction à la tuberculine dans diverses régions géographiques—Sa relation avec la résistance

1. La réaction à la tuberculine a été observée chaque année pendant un délai de neuf à onze ans chez 1.432 sujets témoins et 1.541 Indiens vaccinés, tous ayant initialement présenté une réaction négative à 0,00002 et à 0,005 mg de PPD.

2. Ces Indiens vivaient à Pima Agency, Arizona; Wind River Agency, Wyoming, Turtle Mt. Agency, North Dakota; Rosebud Agency, South Dakota; et dans douze autres collectivités dans l'Alaska du Sud-Est.

3. Les modalités de la réaction à la tuberculine des groupes témoins et des groupes vaccinés avec le BCG ont été classées de façon arbitraire en dix catégories

différentes sur la base de la persistance, de la fluctuation ou de la réversion de cette réaction.

4. Après neuf à dix années d'observation, il a été constaté que la proportion de la sensibilité à la tuberculine persistante et d'un degré élevé a été plus grande chez les témoins que dans le groupe vacciné avec le BCG.

5. Parmi ceux qui présentaient un haut degré de sensibilité à la tuberculine, comme le montrait la réaction à 0,00002 mg. de PPD, un pourcentage faible des témoins et un pourcentage plus élevé des vaccinés ont présenté une réduction du degré de sensibilité à la tuberculine ou un retour à la réaction négative.

6. L'accroissement de la sensibilité à la tuberculine, de 0,005 à 0,00002 mg. de PPD, s'est souvent produit chez les sujets vaccinés qui avaient été soumis à une surinfection par un bacille tuberculeux virulent.

7. La fluctuation de la réaction à tuberculine, comme la réversion de positive à négative, est survenue fréquemment parmi les sujets témoins et les sujets vaccinés à Pima Agency en Arizona.

8. L'instabilité de la réaction à la tuberculine observée chez les vaccinés au BCG résidant à Pima Agency, en Arizona, ne peut être attribuée au faible pouvoir antigène du BCG, mais elle pourrait être en relation avec des facteurs climatiques, comme l'excès d'insolation.

9. Aucune relation n'a été constatée entre l'instabilité de la réaction à la tuberculine et la mortalité par tuberculose parmi les individus résidant à Pima Agency. Parmi les sujets témoins observés, pendant 3.952 homme/heures, 9 sont morts de cette affection, tandis que chez les vaccinés par le BCG observés, soit 4.085 homme/années, un seul est mort de tuberculose. Ce dernier a présenté un phénomène de Koch intense quarante-huit heures après la vaccination et il est mort deux mois plus tard.

Acknowledgment

The assistance of Miss Erma Parr, R. N., in conducting the tuberculin tests is acknowledged with deep appreciation.

REFERENCES

(1) v. Pirquet, C. E.: Allergy, Arch. Int. Med., 1911, *7*, 259, 383.

(2) Debré, R., and Papp, K.: Recherches sur la disparition de la cutiréaction positive à la tuberculine pendant la rougéole, Ann. de. méd., 1926, *19*, 576.

(3) Mitchell, A. G., Wherry, W. B., Eddy, B., and Stevenson, F. E.: Nonspecific factors influencing the reaction of the skin to tuberculin, Am. J. Dis. Child., 1928, *36*, 720.

(4) Lereboullet, P., and Baike, P.: Rougéole et cutiréaction tuberculinique, Arch. de méd. d. enf., 1931, *34*, 701.

(5) Pilcher, J. D.: Local skin reactions in measles and scarlet fever in relation to the intracutaneous tuberculin reaction, Am. Rev. Tuberc., 1935, *31*, 568.

(6) Nalbant, J. P.: The effect of contagious diseases on pulmonary tuberculosis and on the tuberculin reaction in children, Am. Rev. Tuberc., 1937, *36*, 773.

(7) Lelong, M., and Rivalier, E.: Syphilis et tuberculose, l'anergie syphilitique, Compt. rend. Soc. de Biol., 1923, *88*, 327.

(8) Tarantelli, E.: Sull' anergia tubercolinica dei sifilitici, La Riforma med., 1926, *42*, 530.

(9) Nobécourt, P., and Forgeron, H.: La cutiréaction à la tuberculin dans la coqueluche; l'anergie tuberculinique, Arch. de méd d. enf., 1922, *25*, 394.
(10) Bloomfield, A. L., and Mateer, J. G.: Changes in skin sensitiveness to tuberculin during epidemic influenza, Am. Rev. Tubere., 1919, *3*, 166.
(11) Happ, W. M., and Casparis, H. R.: The value of the intracutaneous tuberculin test in extensive tuberculosis, Am. J. Dis. Child., 1922, *23*, 527.
(12) Lincoln, E. M.: Tuberculous meningitis in children, Am. Rev. Tubere., 1947, *56*, 75.
(13) Longcope, W. T., and Pierson, J. W.: Boeck's sarcoid (sarcoidosis), Bull., Johns Hopkins Hosp., 1937, *60*, 223.
(14) Israel, H., Sones, M., Stein, S. C., and Aronson, J. D.: BCG vaccination in sarcoidosis, Am. Rev. Tubere., 1950, *62*, 408.
(15) Stern, R.: Systematische Untersuchungen über die localen Tuberkulin-reaktionen in der Schwangerschaft und im Wochenbett und Schlussfolgerungen hinsichtlich der Diagnosen-und Prognosenstellung, Ztschr. f. Geburtsh. u. Gynäk., 1910, *66*, 533.
(16) Nobécourt, P., and Paray, J.: L'influence de la grossesse sur l'évolution de la tuberculose pulmonaire et pleurale, Presse méd., 1920, *28*, 133.
(17) Lichtenstein, M. R.: Tuberculin reaction in tuberculosis during pregnancy, Am. Rev. Tubere., 1942, *46*, 89.
(18) Conn, R. W.: Effect of pregnancy upon tuberculin reaction, Am. Rev. Tubere., 1942, *46*, 350.
(19) Joussel, A.: La valeur diagnostique des cutiréactions à la tuberculine chez l'adult; et l'anergie accidentelle, Bull. et mém. Soc. méd. d. hôp. de Paris, 1926, *50*, 834.
(20) Westwater, J. D.: Allergy in tuberculosis, Tubercle, 1934, *15*, 543.
(21) Bønsdorff, K.: On variations in sensitiveness to tuberculin after surgical collapse-treatment of pulmonary tuberculosis, Acta tubere. Scandinav., 1938, *13*, 383.
(22) Decressac, G., and Jacqueline, A.: Contribution à l'étude de la cutiréaction à la tuberculine chez les opérés, Compt. rend. Soc. de biol., 1924, *91*, 272.
(23) Ricciardi, L.: Sul comportamento della cutireazione alla tubercolina in rapporto alla vaccinazione jenneriana, Pediatria, 1926, *34*, 421.
(24) Grenet, C.: Action de certain facteurs non-specifiques sur l'intensité de la cutiréaction tuberculinque, Rev. de la tubere. 1935, *1*, 502.
(25) Kepinow, L., and Metalnikow, S.: Glande thyroide et sensibilité des animaux tuberculeux envers la tuberculine, Compt rend.. Soc. de Biol., 1922, *87*, 210.
(26) Schilf, F.: Tuberkulinreaktion und C vitamin, Centralbl. f. Bakt., 1925, *91*, 512.
(27) Heise, F. H., Martin, G. J., and Schwartz, S.: The influence of the administration of vitamin C on blood sedimentation and sensitivity to tuberculin, Brit. J. Tubere., 1937, *31*, 23.
(28) Birkhaug, K. E.: Effect of l-ascorbic acid on the tuberculin reaction in tuberculous animals, Acta tubere. Scandinav., 1939, *13*, 45.
(29) Willis, H. S.: The waning of cutaneous hypersensitiveness to tuberculin, Am. Rev. Tubere., 1928, *17*, 240.
(30) Smith, T.: The vaccination of cattle against tuberculosis, J. Med. Research, 1911, *25*, 1.
(31) Elder, C., and Lee, A. M.: Injection of cattle with *B. tuberculosis* (avian) and results of subsequent tuberculin tests, J. Am. Vet. M. A., 1924, *64*, 440.
(32) Boquet, A.: Substances antihistaminques et réaction tuberculiniques, Ann. Inst. Pasteur, 1943, *69*, 55.
(33) Friedman, E., and Silverman, I.: The effect of antihistamine medication on the tuberculin reaction in children, Am. Rev. Tubere., 1949, *60*, 354.
(34) Crief, L. H., Levine, M. I., and Aaron, T. H.: Inhibition of the tuberculin type reaction by antihistaminic drugs and rutin, Am. Rev. Tubere., 1949, *59*, 701.

(35) Weiser, R. S., Evans, E., St. Vincent, L.: Failure of pyribenzamine to protect against systemic tuberculin shock, Proc. Soc. Exper. Biol. & Med., 1950, *73*, 303.

(36) Sarber, R. W.: Effect of benadryl hydrochloride on the tuberculin reaction in guinea pigs, Am. Rev. Tubere., 1948, *57*, 504.

(37) Graub, M., and Barrist, E. M.: The effect of antihistaminic drugs upon the tuberculin reaction, Am. Rev. Tubere., 1950, *61*, 735.

(38) Harris, S., and Harris, T. N.: Effect of cortisone on some reactions of hypersensitivity in laboratory animals, Proc. Soc. Exper. Biol. & Med., 1950, *74*, 186.

(39) Long, J. B., and Favour, C. B.: The ability of ACTH and cortisone to alter delayed-type bacterial hypersensitivity, Bull., Johns Hopkins Hosp., 1950, *87*, 186.

(40) Carlisle, J. M., Gibson, A., and Schmatolla, E.: Cortisone, Post.-Grad. M. J., 1950, *8*, 113.

(41) Pilcher, J. D.: Diminution in the circulation of the skin a factor in decreasing the cutaneous tuberculin reaction, Am. Rev. Tubere., 1930, *21*, 669.

(42) Brahic, J., and Veyron, J.: Etude comparée de la cutiréaction-tuberculinique et de l'intra-dermo-réaction-histaminique chez les tuberculeux pulmonaires, Compt. rend. Soc. de biol., 1939, *131*, 302.

(43) Howe, J. S.: Daily variations in the tuberculin reaction, Am. Rev. Tubere., 1938, *37*, 264, 273.

(44) Ossoinig, K.: Uber Schwankungen d. Tuberkulinempfindlichkeit nebst einigen Bemerkungen über das Auftreten der Meningitis tuberculosa, Beitr. z. Klin. d. Tuberk., 1926, *63*, 895.

(45) Austrian, C. R.: Observations on children admitted to a tuberculosis dispensary, Tubercle, 1924, *6*, 29.

(46) Lloyd, W. E., and MacPherson, A. M.: A reinvestigation of children previously examined by tuberculin tests, Brit. M. J., 1933, *1*, 818.

(47) Dahlstrom, A. W.: The instability of the tuberculin reaction, Am. Rev. Tubere., 1940, *42*, 471.

(48) Zacks, D., and Sartwell, P. E.: Development of tuberculosis and changes in sensitivity to tuberculin in an institution for the feeble minded, Am. J. Pub. Health, 1942, *32*, 732.

(49) Cayley, C. K.: Personal communication.

(50) Keressturi, C., Rosenberg, H. A., and Park, W. H.: Tuberculin allergy produced by parenteral BCG vaccination, Am. Rev. Tubere., 1937, *36*, 90.

(51) Aronson, J. D., and Palmer, C. E.: Experience with BCG vaccine in the control of tuberculosis among North American Indians, Pub. Health Rep., 1946, *61*, 802.

(52) Aronson, J. D.: Protective vaccination against tuberculosis with special reference to BCG vaccination, Am. Rev. Tubere., 1948, *58*, 255.

(53) Seibert, F. B.: The isolation and properties of the purified protein derivative of tuberculin, Am. Rev. Tubere., 1934, *30*, 713.

(54) Seibert, F. B., and Glenn, J. T.: Tuberculin purified protein derivative, Am. Rev. Tubere., 1941, *44*, 9.

(55) Aronson, J. D.: The purified protein derivative, Am. Rev. Tubere., 1934, *30*, 727.

(56) Aronson, J. D., Parr, E. I., and Saylor, R.: BCG vaccine: Its preparation and the local reaction to its injection, Am. Rev. Tubere., 1940, *42*, 651.

(57) Rich, A. R.: The role of allergy in tuberculosis, Arch. Int. Med., 1929, *43*, 691.

(58) Rich, A. R., and McCordock, H. A.: An enquiry concerning the role of allergy, immunity and other factors of importance in the pathogenesis of human tuberculosis, Bull., Johns Hopkins Hosp., 1929, *44*, 273.

(59) Dupres, C.: Sur les relations entre l'allergie et l'immunité dans l'infection tuberculeuse, Compt. rend. Soc. de biol., 1934, *117*, 834.

(60) Rothschild, H., Friedenwald, J. S., and Bernstein, C.: The relation of allergy to immunity in tuberculosis, Bull., Johns Hopkins Hosp., 1934, *54*, 232.

(61) Lewis, P. A., and Loomis, D. J.: Ulcerative types as determined by inheritance and as related to natural resistance against tuberculosis, J. Exper. Med., 1928, *47*, 449.

(62) Haudurot, P.: Inventaire et Description des Bacillus Paratuberculeux, Masson et Cie, Paris, 1946.

(63) Aronson, J. D., Saylor, R. M., and Parr, E. I.: Relationship of coccidioidomycosis to calcified pulmonary nodules, Arch. Path., 1942, *34*, 31.

(64) Mayer, E.: Experimental study of action of ultraviolet light on the intradermal tuberculin reaction, Am. Rev. Tubere., 1920, *4*, 100.

(65) Valtis, J., and Portret, A.: De l'influence du facteur "peau" sur la cutiréaction à la tuberculine., Compt. rend. Soc. de biol., 1927, *97*, 345.

(66) Talon-Chauveau, M., Valtis, J., and Talon, L. R.: De l'influence de l'irradiation solaire sur l'allergie dermique à la tuberculine, Compt. rend. Soc. de Biol., 1927, *97*, 683.

THE IMPORTANCE OF THE TUBERCULIN TEST IN THE DIFFERENTIAL DIAGNOSIS OF PULMONARY LESIONS[1]

C. EUGENE WOODRUFF AND W. LEONARD HOWARD

(Received for publication May 18, 1950)

Widespread use of roentgenographic surveys for the early discovery of pulmonary disease has greatly increased the number of diagnostic problems in cases which are referred to tuberculosis sanatoriums. A few years ago the usual patient entered a sanatorium because he had been sick enough to consult a physician; his physical examination produced such prominent findings that the diagnosis was readily made and he was convinced of the need for treatment. Today, in increasing numbers patients are sent to a sanatorium merely because a chest film has revealed shadows suggestive of tuberculosis. In a certain proportion of cases this roentgenographic diagnosis of tuberculosis will be in error. The result is a needless subjection of the patient to mental perturbation and of the public or private purse to a drain for unwanted hospitalization. To reduce to a minimum this period of needless hospitalization, it is necessary for the sanatorium staff to make proper use of all possible diagnostic aids. In the present paper an evaluation is made of the part played by the routine tuberculin test in speeding up the diagnosis of problem cases referred to a municipal tuberculosis sanatorium.

MATERIAL AND METHODS

During the past ten years an attempt has been made to give a quantitative tuberculin test (1–3) to all patients admitted to the adult division of the Wm. H. Maybury Sanatorium. All of these patients had been hospitalized because of either the roentgenographic or the clinical diagnosis of tuberculosis.

The intracutaneous tests, beginning with 0.1 ml. of a 1:10,000 dilution of tuberculin OT[2] were administered by the technologist at the time that blood was taken for a blood count. The test was interpreted at the end of forty-eight hours; an area of induration 5 mm. or more in diameter was considered a positive reaction. Patients who failed to react to the 1:10,000 dilution were retested after forty-eight hours with the 1:1,000 dilution; if the reaction was still negative, they were further tested with the 1:100 dilution and finally with the 1:10 dilution of tuberculin. The various dilutions were kept in transparent glass serum bottles. Before each use the tuberculin was carefully examined for any evidence of bacterial or fungal growth. The dilutions may be used for several weeks if they remain uncontaminated.

The sputum of each newly admitted patient was "combed" for tubercle bacilli by ex-

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[2] The tuberculin used in this study was donated by Parke, Davis and Company of Detroit. Two liters of undiluted OT were obtained in 1939 through the kindness of the late Dr. L. T. Clark. Dilutions from this original batch have been used since that time. There has been no appreciable change in potency of the OT.

amining at least 3 direct and 2 concentrated smears and by making at least one culture, if the sputum had not previously been proved positive for tubercle bacilli.

In compiling results of the tests, positive reactors to the 1:10,000 dilution of tuberculin were considered as being in the "10,000" sensitivity group. Those patients who failed to react to 1:10,000 OT but showed a positive reaction to the 1:1,000 dilution were placed in the "1,000" sensitivity group, and so on for the other dilutions. Patients who *failed* to react to the 1:10 dilution of tuberculin were considered to be anergic and were allocated to a "0" sensitivity group.

The present study is based on data obtained from patients admitted during the two and one-half year period from January 1, 1947 to July 1, 1949.[3] During this interval 1,395 patients were newly admitted to the adult division. Because of the premature discharge or death of some of the patients, however, the laboratory data are incomplete in 42 instances, leaving 1,353 cases for analysis.

RESULTS

In table 1 may be seen the relative number of patients found in each sensitivity group. As shown, the cumulative percentage of patients reacting to the first two dilutions of tuberculin is 91.8. This information from the tuberculin tests is available on the fourth day after admission, usually before the initial sputum

TABLE 1

Number and Per Cent of Patients in Different Tuberculin Sensitivity Groups

SENSITIVITY GROUP	"10,000"	"1,000"	"100"	"10"	"0"	TOTAL
Number in group	916	326	50	23	38	1,353
Per cent	67.7	24.1	3.7	1.7	2.8	100
Cumulative per cent	67.7	91.8	95.5	97.2	100.0	

examinations have been completed. Thus, in a large majority of cases the positive tuberculin reaction gives the clinician at least presumptive evidence of tuberculous infection regardless of what the sputum findings may prove to be.

The data from table 1, as shown graphically in figure 1, indicate a progressive decrease in the number of patients in each sensitivity group until the fifth or "0" group is reached. With this group there is a definite increase in numbers, the reason being that this "0" or anergic group contains such a large proportion of nontuberculous cases. Actually the proportion of anergic patients admitted to a municipal tuberculosis sanatorium such as Maybury is considerably greater than the indicated 2.8 per cent. As mentioned above, 42 patients had to be excluded from the present study because either death or discharge of the patient occurred before his laboratory examinations were completed. In 16 of the 42, the sputum was positive for acid-fast bacilli on direct smear, the cutaneous reaction was negative to at least the first dilution of tuberculin, but death occurred before all of the tuberculin tests could be completed. Almost certainly these 16 patients

[3] A study based on patients admitted from January 1, 1945 to January 1, 1947 has been published (4).

belong in the anergic group. If included, they would bring the total for the group to 54, or 3.9 per cent.

Data obtained from the 1,353 patients are arranged in table 2 to make possible a differentiation between patients whose tuberculous disease was readily diagnosed by finding acid-fast bacilli in smears of the sputum; those in whom it was necessary to wait for a culture of the sputum or gastric contents before the diagnosis was confirmed; and, finally, those patients in whom the bacteriologic diagnosis of tuberculosis was never made.[4] In attempting to reach an early decision as to whether or not a newly admitted patient should remain in the sanatorium, it is evident that the examination of sputum smears gave the answer in 772 cases, or 57 per cent of the total. There remains 43 per cent of the cases in which study of the sputum was of no immediate help in making the differential diagnosis. In 246 instances, or 18.2 per cent, active tuberculosis was eventually

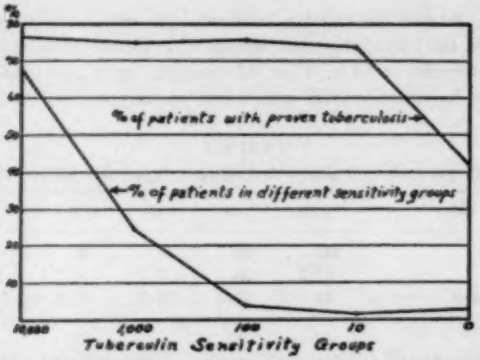


FIG 1. Percentage of patients in different sensitivity groups (lower curve) and percentage of patients in each sensitivity group who had bacteriologically proved tuberculosis (upper curve).

diagnosed by sputum cultures, but this usually meant a delay of at least six weeks. Since a positive reaction to 1:1,000 or 1:10,000 OT is considered suggestive of active tuberculosis, the administration of tuberculin tests at the same time that study of the sputum was proceeding reduced the urgent diagnostic load in this series from 43 per cent of the total to the relatively few cases indicated in table 2 in the double-lined box, only 51 cases or 3.8 per cent of the total.

While the fact should be emphasized that a positive reaction to 1:1,000 or 1:10,000 OT is merely suggestive and not diagnostic, nevertheless the clinician may feel more at ease about the possible dangers of sanatorium exposure to tuberculosis if he is dealing with a patient who is already hypersensitive to tuberculin. The actual diagnostic significance of a positive reaction to these

[4] It should be noted that in all of the cases included in the present study sputum specimens were obtained before the patient had had any antimicrobial therapy.

dilutions will depend upon the expected incidence of positive reactors in a given age group and this in turn will vary in different parts of the country. In the Detroit area the expected incidence is approximately 19 per cent in the 10–19 age group and rises to more than 44 per cent in individuals 30 years of age or older (5).

In table 3, obtained from the data in table 2, it is indicated that the proportion of bacteriologically proved cases of tuberculosis remains almost constant through the first four sensitivity groups but falls abruptly in the fifth or "0" group.

TABLE 2

Classification of 1,353 Patients according to Tuberculin Sensitivity and Sputum Findings

TUBERCULIN SENSITIVITY GROUP	TOTAL		SPUTUM FINDINGS IN PATIENTS					
			Smear positive for acid fast bacilli		Smear negative; culture positive for tubercle bacilli		Smear and culture negative for tubercle bacilli	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total	1,353	100	772	57.0	246	18.2	335	24.8
"10,000"	916	100	527	57.5	176	19.2	213	23.3
"1,000"	326	100	185	56.7	59	18.1	82	25.2
"100"	50	100	32	64.0	6	12.0	12	24.0
"10"	23	100	14	61.0	3	13.0	6	26.0
"0"	38	100	14	36.9	2	5.3	22	57.8

TABLE 3

Number and Per Cent of Patients with Bacteriologically Proved Tuberculosis in Different Sensitivity Groups

TUBERCULIN SENSITIVITY GROUP	TOTAL PATIENTS	PROVED TUBERCULOSIS	
		Number	Per cent
Total	1,353	1,018	74.5
"10,000"	916	703	76.7
"1,000"	326	244	74.9
"100"	50	38	76.0
"10"	23	17	73.9
"0"	38	16	42.1

The data are shown graphically in the upper curve of figure 1. Thus, in the Detroit area there is a probability of approximately three to one that the case diagnosed roentgenographically as having pulmonary tuberculosis will actually be proved to have that disease even though the patient may only react to 10 mg. of 1:10 OT. If the patient *fails* to react to 1:10 OT, however, the chances are less than even that the diagnosis of tuberculosis will be confirmed.

With the decrease in sensitivity to tuberculin, there is a rather marked decrease in the proportion of patients requiring culture of the sputum for a bac-

teriologic diagnosis of their tuberculosis (figure 2). Conversely, the same anergic or partially anergic patients show the greatest proportion of "smear-positive" cases, as indicated in table 4 and figure 3. Case analyses of the anergic patients reveal that for the most part they fall into either one of two categories: They are critically ill with tuberculosis and have sputum which is loaded with

TABLE 4

Number and Per Cent of Proved Tuberculous Patients with Acid-fast Bacilli in Smears of the Sputum

TUBERCULIN SENSITIVITY GROUP	TOTAL	SMEAR POSITIVE FOR ACID-FAST BACILLI	
		Number	Per cent
Total	1,018	772	75.8
"10,000"	703	527	74.9
"1,000"	244	185	75.8
"100"	38	32	84.2
"10"	17	14	82.4
"0"	16	14	87.5

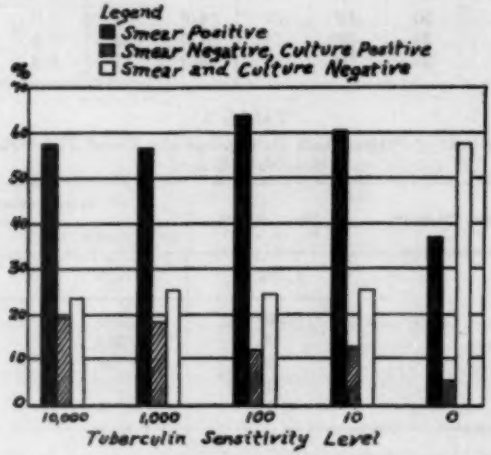


FIG. 2. Tuberculin sensitivity as related to sputum findings in newly admitted sanatorium patients.

tubercle bacilli, or they do not have tuberculosis at all. A probable reason for the large number of tubercle bacilli in the sputum of patients in the first category is the fact that in the anergic patient tubercle bacilli are able to grow in contact with the living tissue cells, as well as on the walls of tuberculous cavities (6).

Aside from the sputum findings, a further differentiating factor in the anergic

group is the clinical condition of the patient. As is well known, the highly allergic tuberculous patient may or may not have serious symptoms. If anergic, however, the tuberculous patient is nearly always critically ill. Among the 38 patients in the "0" sensitivity group in the present series, 17 were finally proved to have tuberculosis. All 17 were critically ill in contrast to the 21 remaining patients, none of whom was seriously ill. Fourteen of the 17 patients had acid-fast bacilli in the sputum in large numbers. In 2 cases culture of the sputum was necessary before tubercle bacilli could be demonstrated; one patient died of miliary tuberculosis and meningitis, and tubercle bacilli were never recovered from his sputum.

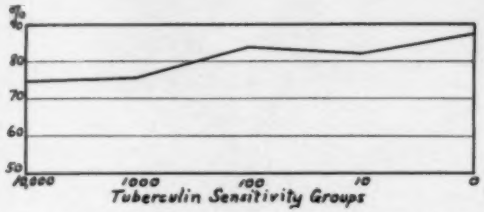


FIG. 3. Percentage of proved tuberculous patients with acid-fast bacilli in smears of the sputum.

TABLE 5

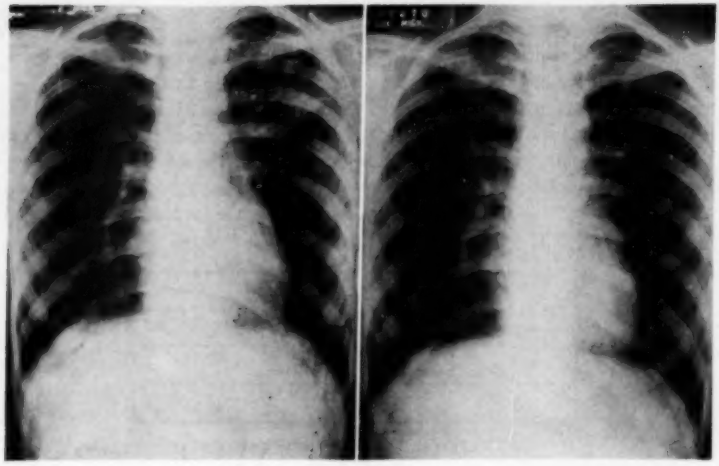
Final Diagnoses for 40 Patients in the "100," "10," and "0" Sensitivity Groups; Sputum Negative for Tubercle Bacilli

Diagnosis	*Number of Patients*
Pulmonary fibrosis and emphysema, including silicosis	13
Bronchopneumonia and other atypical pneumonias	8
Lung abscess	5
Bronchiectasis	4
"Dry" pleurisy	3
Bronchiogenic carcinoma	2
Sarcoidosis	2
Fungal disease	2
Miliary tuberculosis with meningitis	1
	40

In fact, all of the anergic tuberculous patients died within a period of a few weeks after their admission to the sanatorium, with one exception. This particular patient recovered after energetic treatment with streptomycin. Her recovery included a reversion from the anergic state, as demonstrated by the ability to react positively to the 1:1,000 dilution of tuberculin.

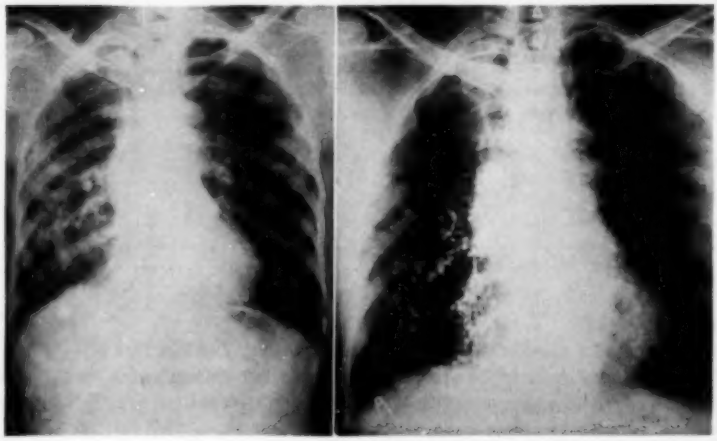
As shown in the right-hand column of table 2, there were 40 anergic or partially anergic patients in whose sputum tubercle bacilli could not be demonstrated. The final diagnoses for these patients are listed in table 5.

The 2 following case reports are presented as examples of the contribution of the tuberculin test to the solution of difficult diagnostic problems.



Case 1

FIG. 4. (Left). Roentgenogram taken on admission to the sanatorium
FIG. 5. (Right) Roentgenogram taken five weeks after admission



Case 2

FIG. 6. (Left). Roentgenogram taken on admission to the sanatorium
FIG. 7. (Right). Bronchogram

CASE REPORTS

Case 1. A 15-year-old white school girl was admitted with the complaint of dry cough and low-grade fever for a period of eight weeks. Two weeks before admission the roentgeno-

graphic diagnosis of tuberculosis was made. The film made on admission to the sanatorium was interpreted as showing a moderately advanced tuberculous process of mixed type in the upper third of the left lung (figure 4). Physical examination revealed no abnormalities other than slight dullness over the left apex, dental caries, and infected tonsils. The total leukocyte count was 15,100 per cu. mm. with 84 per cent neutrophils. The patient failed to react to all dilutions of tuberculin including the 1:10. Three specimens of sputum and one gastric lavage were cultured for tubercle bacilli, with negative results. The patient's temperature never went above 100°F. and was subnormal most of the time. A roentgenogram obtained five weeks after admission showed marked clearing of the lesions in the left upper lobe (figure 5). The patient was discharged with the final diagnosis of atypical pneumonia.

Case 2. A 70-year-old Negro housewife was admitted because of a "positive" chest roentgenogram. The film had been obtained because of contact with a case of active tuberculosis. The patient had "not been sick for twenty-five years." Roentgenographic examination on admission to the sanatorium revealed a far advanced tuberculous process, mostly productive in type, throughout all of the right lung, with no definite evidence of cavitation (figure 6). Except for signs of senility and crepitant rales over most of the right lung, physical examination was essentially negative. The total leukocyte count showed 14,000 cells per cu. mm. with 78 per cent neutrophils. The patient failed to react to all dilutions of tuberculin including 1:10. Her temperature was consistently normal or subnormal. Eight sputum examinations, including two cultures, were negative for tubercle bacilli. A bronchogram showed saccular bronchiectasis of the right middle lobe and the superior segment of the right lower lobe (figure 7). The patient was discharged with the final diagnosis of bronchiectasis.

DISCUSSION

Prior to 1940 the tuberculin test was commonly used in case-finding surveys. Such surveys, however, yielded on the average only 2 cases of active tuberculosis for every 100 positive reactors to tuberculin (7, 8). This low yield has brought the tuberculin test into disrepute for use in primary surveys, but does not in the least minimize the importance of testing with tuberculin those persons whose roentgenograms show suspicious shadows. More than 90 per cent of these individuals will react to the 1:10,000 or the 1:1,000 dilution of tuberculin and a positive cutaneous reaction to one of these dilutions, taken in conjunction with the "positive" roentgenogram, affords presumptive evidence in favor of active tuberculous infection.

To be of the most value to the clinician, it is necessary that the examination of a patient's allergic condition be started on the day he arrives at the sanatorium instead of utilizing the tuberculin test only as a last resort after studies of the sputum have been completed. If started promptly, definitive information from the tuberculin tests will be available long before results from cultures of the sputum or gastric contents.

The tuberculin tests should be continued in each given case until either a positive reaction is obtained or the patient is shown to be anergic. D'Arcy Hart (1) has indicated that, if the critically ill (patients with severe toxemia) are omitted from consideration, the failure to react to the 1:10 dilution of tuberculin may be taken as meaning that a patient does not have tuberculosis, with an expected error of only 2 per cent. Likewise, Sweany (9) found that "The absence of tuberculous disease is almost certain (97.1 per cent) in uncomplicated cases negative to the 1:100 dilution." Lichtenstein (10), in a survey of more

than 11,000 sanatorium patients, found that after excluding the very ill and the senile patients there were only 142 who failed to react to the 1:10 dilution of tuberculin. Of these, all but 4 were found to be nontuberculous. These papers state in another way what has been emphasized in the present study, namely, that the anergic tuberculous patient is nearly always critically ill. In the 2 case reports detailed above, the very suggestive evidences of tuberculosis seen on the admission roentgenograms were negated by the fact that the patients, although completely anergic to tuberculin, were not seriously ill. This combination of findings has helped in many cases to decrease by several weeks the period of hospitalization needed before a differential diagnosis could be reached.

Tuberculin OT rather than PPD was used in the present study partly because of the ready availability of the former; also because with OT the various tenfold dilutions of the original product are made so easily. It should be noted that the sharp "break" in the incidence of tuberculosis, as indicated in table 3, does not occur until the fifth or "0" sensitivity group is reached and that this "0" group is not differentiated by the standard second-strength dose of PPD.

If an accurate determination of cutaneous sensitivity to tuberculin is made on a series of newly admitted sanatorium patients, the clinical staff will be rewarded in the following ways: (*1*) The positive cutaneous reaction to 1:10,000 or 1:1,000 OT obtained in the great majority of patients will give at least presumptive evidence of active tuberculous infection. (*2*) In the diagnostic study of those cases with a low level of tuberculin sensitivity, the fact that the truly tuberculous patient is almost always critically ill may be used to advantage. Thus, if one encounters an anergic patient who appears healthy, who perhaps walked to the sanatorium or to the clinic office, the diagnosis of tuberculosis will be considered very dubious regardless of how suggestive the roentgenogram may appear. (*3*) Finally, the clinician will remember that anergic or partially anergic tuberculous patients are more likely to have acid-fast bacilli in smears of the sputum than are highly allergic patients. If the roentgenogram of a completely anergic patient shows definite cavitation and adequate specimens of his sputum fail to show acid-fast bacilli in the direct smears, the possibility of tuberculosis may be dismissed.

SUMMARY

Data obtained from 1,353 sanatorium patients have been analyzed in an attempt to assess the value of the quantitative tuberculin test in the differential diagnosis of pulmonary lesions. The data indicate that tuberculin tests started at the same time that the admission sputum studies are being done may be of considerable aid to the clinician in reaching a proper diagnosis.

SUMARIO

La Importancia de la Reacción a la Tuberculina en el Diagnóstico Diferencial de las Lesiones Pulmonares

Los datos obtenidos de 1,353 enfermos de sanatorios han sido analizados con mira a justipreciar el valor de la prueba tuberculínica cuantitativa en el

diagnóstico diferencial de las lesiones pulmonares. Los datos indican que las tuberculino-reacciones iniciadas al mismo tiempo que los estudios del esputo al ingreso pueden resultar de mucha ayuda al clínico para llegar al diagnóstico acertado.

RESUME

L'importance du test à la tuberculine pour le diagnostic différentiel des lésions pulmonaires

Les observations faites sur 1.353 malades hospitalisés en sanatorium ont été analysées pour déterminer la valeur du test quantitatif à la tuberculine dans le diagnostic différentiel des lésions pulmonaires. Ces observations indiquent que les tests à la tuberculine commencés au moment de l'admission, en même temps que les examens de crachats sont effectués, peuvent représenter pour le clinicien une aide considérable pour établir un diagnostic.

REFERENCES

(1) Hart, P. D.: The value of tuberculin tests in man, Med. Research Council, Spec. Rep. Series, No. 164, London, 1932.
(2) Furcolow, M. L., Hewell, B., and Nelson, W. E.: Quantitative studies of the tuberculin reaction: III. Tuberculin sensitivity in relation to active tuberculosis, Am. Rev. Tuberc., 1942, *45*, 504.
(3) Woodruff, C. E.: The quantitative tuberculin test, Am. Rev. Tuberc., 1947, *55*, 488.
(4) Woodruff, C. E.: On the verification of the diagnosis of tuberculosis, Pub. Health Rep., 1948, *63*, 184.
(5) Douglas, B. H., and Harmon, G. E.: Results obtained in an extensive tuberculosis case-finding program in a large city, Am. J. Pub. Health, 1939, *29*, 583.
(6) Brosius, W. L., and Woodruff, C. E.: The effect of sensitivity on the distribution of tubercle bacilli in tuberculosis, Am. Rev. Tuberc., 1944, *50*, 473.
(7) Douglas, B. H.: X-ray findings in tuberculin reactors and non-reactors, Am. Rev. Tuberc., 1939, *40*, 621.
(8) Myers, J. A.: The establishment and use of fundamental procedures in tuberculosis control, Pub. Health Rep., 1946, *61*, 1563.
(9) Sweany, H. C.: The tuberculin test: Its use, limitations and future possibilities in diagnosis, Am. Rev. Tuberc., 1947, *56*, 135.
(10) Lichtenstein, M. R.: Nonreactors to tuberculin: An analysis in a large sanatorium, Am. Rev. Tuberc., 1947, *56*, 198.

ENDOTHELIOMA (MESOTHELIOMA) OF THE PLEURA[1,2]

A Review with a Report of Seven Cases, Four of Which Were Extirpated Surgically

LEW A. HOCHBERG

(Received for publication July 19, 1950)

INTRODUCTION

In recent years a number of reports have been published on pleural endothelioma stressing its uncommonness, questioning its origin, noting its controversial pathology, calling attention to its variegated clinical manifestations, and even denying its very existence. Consequently, any information which can be added concerning the identification and classification of these tumors should prove helpful. In the present report the writer will present 4 cases in which a primary tumor of the pleura was removed surgically; one in which the presence of the tumor was established by exploration and subsequently at necropsy; and an additional 2 in which necropsy was performed. The observations made in these 7 cases has led the writer to believe that primary endothelioma of the pleura exists and is not highly malignant in its early stages, and that these tumors are readily amenable to surgical extirpation.

The term most often applied to the tumors (endothelioma) implies that they arise from the endothelial tissues of the lymphatics, blood vessels, or lining cells of the pleura. Those who stress the point that the pleural endothelium is embryologically derived from the epithelial component of the mesoderm have generally preferred to employ the more inclusive term "*mesothelioma*." In common with Robertson (57), a number of writers assume that there is no such entity as an endothelioma or mesothelioma of the pleura, that all primary pleural tumors should be classified as sarcomas, and that all other tumors are secondary to neoplasms of the lung or other unrecognized malignant tumors.

Willis (72) also classifies these tumors under the heading of "secondary tumors in serous cavities masquerading as primary ones" and states:

> *Pathological misdiagnoses* have frequently been made in cases of secondary disease from unrecognized primary growths elsewhere. In 1934 I reviewed many reported cases of supposedly primary neoplasms of serous membranes and concluded that most, if not all, of them were only examples of serosal disease secondary to undiscovered tumors, usually in the neighboring viscera. My perusal of the more recent literature and my own later experiences have confirmed that opinion.

While there is no doubt that a number of secondary tumors of the pleura have been misdiagnosed as primary endotheliomas of the pleura, the consensus of competent pathologists is not in accord with Willis. Some investigators have

[1] From the Departments of Thoracic Surgery, Kings County, Caledonian, Brooklyn Jewish, and Bushwick Hospitals, Brooklyn, New York.

[2] The preparation of this report was made possible through a grant by the K. B. Weissman Foundation of New York City.

maintained that these tumors are carcinomas arising from islands of displaced lung tissue, aberrant nests of pulmonary epithelium, in the pleura (Ribbert (56), Fischer-Wasels (25)). Other investigators identified the site of origin of these tumors in other parts of the tissue and therefore proposed different names for them: *lymphangitis proliferans* (Fränkel (27)), *endothelial carcinoma* (Schulz (63)), *adeno-endothelioma, sarco-endothelioma, fibro-endotheliosarcoma, endothelioma carcinomatodes, lymphangio-endothelioma, perithelioma, fibro-endotheliosis* of the pleura, and *pleuroma*. Saccone and Coblenz (59) argue that the term "pleuroma" avoids the ambiguities occasioned by other designations and indicates merely the site of origin. It falls short in nomenclature, however, in that it does not identify the cell from which the tumor arises, nor does it take into

TABLE 1

Incidence of Endothelioma in Collected Autopsy Series

AUTHOR	INSTITUTION	YEAR OF REPORT	NUMBER OF ENDOTHELIOMAS	NUMBER OF AUTOPSIES	PER CENT
Seydel	Path. Inst. of Munich	1910	2	10,829	0.02
Keilty	Univ. Hosp. of Philadelphia	1917	9	5,000	0.18
Bayne-Jones	Johns Hopkins Hospital	1919	2	5,000	0.04
Robertson	University of Minnesota	1924	3	3,000	0.10
Makry-Rauchberg	Prague	1937	7	5,345	0.13
Sørensen	University of Copenhagen	1938	4	5,680	0.07
Saccone and Coblenz	Metropolitan Hospital, N. Y.	1943	2	1,000	0.20
Postoloff	Toronto General Hospital	1944	7	7,878	0.09
Unpublished data	Jewish Hospital of Brooklyn, N. Y.	1949	4	5,760	0.07
Unpublished data	Bushwick Hospital, Brooklyn, N. Y.	1949	0	550	0.00
Unpublished data	Kings County Hospital, Brooklyn, N. Y.	1949	3	10,000	0.03
Totals			43	60,042	0.07

consideration the fact that similar tumors may arise in other serosal membranes such as the pericardium and peritoneum.

Pleural endothelioma is of infrequent occurrence. In 1909 Patterson (53) collected only 96 cases reported in the literature up to that time. Five years later Rosenbaum (58) stated that he could find but 60 authentic cases reported in the literature. At the Jewish Hospital of Brooklyn, 4 pleural endotheliomas were encountered in 5,760 necropsies. At the Bushwick Hospital, in a series of 550 necropsies, no cases of endothelioma of the pleura were encountered; and at Kings County Hospital, 3 cases were observed in 10,000 necropsies performed in the last twelve years. In a series of 60,042 necropsies collected from various sources (table 1), pleural endotheliomas were found in 43 cases, or an autopsy percentage of 0.07.

GENESIS OF PLEURAL ENDOTHELIOMA

The morphologic variations in cytology of these tumors have been the chief basis for dispute concerning their derivation. Of the theories proposed, on the one hand is the extreme view that all primary pleural neoplasms are varieties of sarcoma, no matter what may be their histologic appearance. This theory is based upon the probability that all possible sources of origin are mesenchymal (D'Allesandro (17), Birch-Hirschfeld (10), Ziegler (77)). On the other hand, it must be pointed out that other investigators have been impressed by the carcinomatous tendencies of endotheliomas. Indeed, cells resembling epithelial cells are found not infrequently, if not characteristically, in carefully studied cases of endothelioma of the pleura. According to another extreme view, because cells of these tumors show such marked resemblance to epithelial cells, it is concluded that these new growths originate in the bronchial epithelium and are therefore secondary tumors of the pleura.

In order to explain the nature of these tumors, it is necessary to consider the origin of the parent tissue from which they arise. According to the Celom theory of the development of the pleura propounded by the Hertwig brothers (34) and universally accepted as an explanation for the origin of the pleura, this serosal tissue is regarded as mesodermal in origin.

The embryologic background of the pleura may be briefly outlined as follows:

The middle-germ layer, the mesoderm, arises from the ectodermal and entodermal layers. The mesoderm soon splits into two lamellae, one fusing with the ectoderm to give rise to the somato-pleura while the other unites with the entoderm to form the splanchno-pleura. Further differentiation of the somatic mesoderm gives rise to voluntary muscle, whereas the visceral mesoderm gives rise to the cellular lining of the serous cavities (pleura, pericardium, and peritoneum) and the genitourinary tract. The mesenchymal component of the mesoderm develops into lymph vessels, blood vessels, involuntary muscle, connective tissue, bone, cartilage, red blood cells, and probably white blood cells as well, thus having cytologic multipotential properties.

These embryologic considerations have been extensively applied in the attempt to explain the origin and nature of pleural endotheliomas. The epithelial relationship of the serosal cells lining the great body cavities would seem to establish the capacity of these cells to manifest certain functions characteristic of epithelium. Moreover, tissues having prominent glandular function may be derived from the epithelial component of the mesoderm. Hence, the alveolar structures and secretory cells seen in endothelioma of the pleura are to be taken as manifestations of the basic epithelial relationship of the serosal lining cells. By virtue of the multipotentialities of the cells lining the pleura, any tumor arising from them may present a variety of cellular features and formations. This possibility prompted a number of investigators, Klemperer and his associates (41, 42), Postoloff (54), and others to advocate the "unitarian" view of the origin of pleural endotheliomas.

While most writers generally agree that the endothelioma is a primary tumor of the pleura, there is no unanimity of opinion as to the specific part of the pleura

which gives rise to these neoplasms or what constitutes the histopathologic picture of the tumors. Some are of the opinion that the tumors have their origin in the endothelium of the subpleural lymphatics; others subscribe to the view that they arise from the endothelium lining the blood vessels of the pleura; and still others believe that the tumors arise from the lining cells of the pleura. There is no doubt that the cytologic variability of these tumors can be cited in support of any one theory. The authorities who subscribe to the unicellular theory of origin favor the view that endothelioma of the pleura originates exclusively from the endothelial cells lining the pleural cavity (Krumbein (43), Fischer (24), Kaufmann (39a), Saccone and Coblenz (59). In support of this theory it may be pointed out that: (*1*) there is not sufficient evidence to warrant the assumption of any other origin; (*2*) the mesenchymal component of the mesoderm is the source of the lining cells of all lymph vessels but does not give rise to epithelial structures; and (*3*) the alveolar structure and the epithelium-like appearance of the cells often seen in these tumors would seem to be explained most satisfactorily on the basis of the embryologic derivation of the parent lining cells, i.e., from the epithelial component of the mesoderm. While these arguments in favor of the unicellular theory are valid, they are somewhat negativistic and do not completely deny the possibilities of origin from the other endothelial cells in the pleura.

PATHOLOGY

Endothelioma may arise from the visceral or parietal pleura and two forms have been recognized: (*1*) a circumscribed tumor which appears to spring from the surface of the pleura; and (*2*) a diffuse growth which is of variable thickness and presents an uncertain focus of origin. The circumscribed tumor is a local process with a vascular surface. The neoplasm is thus alternately yellowish-gray and dark red. The cut surface is yellowish with prominent vascular markings towards its periphery and has a rubbery consistency. The lung tissue about the tumor may show some discoloration as a result of compression by the tumor. The diffuse endothelioma of the pleura is the more commonly encountered form of neoplasm. In the early stages the diffuse growth, in all likelihood, has some of the features characteristic of the circumscribed pleural endothelioma. This is purely conjecture, since no case observed at this stage has ever been described. In due time, as the tumor grows, the pleural membrane may become transformed into an extensive and irregular mass of tumor tissue. Examination of the intrathoracic contents at this stage reveals a variable amount of fluid (serous, serohemorrhagic, or hemorrhagic) within the homolateral pleural cavity. When this is removed, a collapsed and contracted lung is revealed, the major portion of which is encased in a pinkish-gray, firm hull. Scattered irregularly over the surface of this tissue are many nodular areas or plaques which are of the same color and consistency as the neoplasm. The thickest part of the tumor is generally located in the diaphragmatic region. Along the mediastinal aspect of the lung, the visceral and parietal pleurae may be so firmly united as to be inseparable and to necessitate removal *en masse*. In the late stages the mediastinal lymph

nodes are usually involved in the neoplastic disease. They are enlarged, firm, and of the same general appearance and consistency as the pleural tumor itself. Not infrequently the chest wall, diaphragm, pericardium, and other structures on the homolateral side show metastatic involvement. The contralateral lung is usually emphysematous. When the diseased lung is cut across, the pleura is found to be many times its normal thickness and the subjacent lung tissue shows some neoplastic involvement. On rarer occasions the underlying lung may also contain metastatic deposits.

It has been stated that, because of the unusual density of the neoplastic process and the marked thickness of the pleura toward the diaphragmatic region, together with the observed greater incidence of pleural nodules at that site, the disease was initiated in the region of the base of the lung. In 4 of the 7 cases presented in this paper, the neoplastic process was known definitely not to have arisen in that area. In the other cases the site of origin was apparently in the region of the lower half of the thorax. The inference is that these tumors do not always arise from the pleura in the lower part of the thorax. The two observations may be correlated in recognizing the fact that, regardless of its site of origin, as the primary tumor grows it sheds cells into the pleural cavity which settle in the most dependent part of the pleural cavity, attach themselves to the pleura, and then grow as tumor transplants. As these tumors may spread by continuity, it is not unreasonable, therefore, to assume that the growth of the tumor implants will enhance the pleural thickening in the region of the base of the lung. The acceptance of this view would abrogate previous assumptions that this tumor process is of multicentric origin and that its origin is necessarily toward the base of the lung.

Histologic findings: Although the histology of endothelioma of the pleura is remarkably variable, with numerous widely differing descriptions published in the literature, there are certain features which are generally regarded as characteristic of this tumor. First, one must recognize the two distinct forms previously described: the localized, and the diffuse, pleural endothelioma.

According to Stout and Murray (65), the two forms present widely different histopathologic appearances. These writers state:

> . . . one of these is distinctly of an epithelial appearance [the diffuse] and consists of solid cords or hollow tubes of cells which sometimes seem to secrete a mucinous material. The other tissue assumes the appearance of a fibrosarcoma, spindle cells arranged in bundles, often with reticulin or collagen fibers between them. The epitheloid elements sometimes have suggested the hyperplastic proliferation of vascular endothelium when the cells assume a rounded or polygonal form, but more often seem truly epithelial with cuboidal or cylindrical cells arranged about lumens. . . . The localized tumors, on the other hand, do not have the epithelioid elements but seem more like fibroma or fibrosarcoma.

The histopathologic appearances are further modified by the particular tissue from which they have taken origin: pleura, lymphatics, or blood vessels; so that there are added difficulties in a classification of the atypical tumor.

The cells comprising the neoplasm are generally of epithelioid character, moderate in size, and may be either round, polyhedral, flat, or exceptionally

spindle-shaped. Their nuclei are most often hyperchromatic and vesicular and may contain one or more nucleoli. In other instances the nuclei may be very faint. In some cells the cytoplasm is quite abundant. The pleura often shows a fibrosis, in which tissue nests of neoplastic cells are present. This thickening of the pleura is the result of desmoplastic reaction. Frequently the fibrosis is so extensive as to give the neoplastic process a scirrhous appearance. The stroma may also show extensive hyaline degeneration. Within the same tumor the cells may manifest notable pleomorphism with variation in size, shape, and activity. Giant cells, too, may be encountered. As Krumbein (43) has pointed out, occasionally one may find concentrically layered bodies remindful of corpora amylacea.

Saccone and Coblens (59) have observed that the nuclei of the tumor cells have a finely granular chromatin and, more characteristically, a distinct nuclear membrane. In one of their cases these writers noted the presence of innumerable small, round or oval, "empty" spaces which at first were thought to be fat vacuoles. These structures varied greatly in size from very minute forms to spaces three or four times the diameter of the surrounding cells. The "empty" spaces were most numerous in that part of the tumor which appeared most malignant. More recently Postoloff (54) described other unusual features of pleural endotheliomas. Within the same block of tissue, adjacent sections showed changes resembling a medullary carcinoma, epithelial cells suggestive of scirrhous carcinoma, and large fibroblasts resembling a sarcoma. The most striking feature of the tissue was the presence of an osteoid matrix, detectable only upon histologic examination. The osteoid matrix in the case reported by Postoloff was present in the secondary nodules within the contralateral lung as well as in the parent tumor. Postoloff believes that bone formation is not the result of local conditions in the pleura but is an inherent developmental property of the tumor tissue, this property being in accordance with the theoretical potentialities of the mesodermal cell. Such observations serve to emphasize the fact that pathologic diagnosis of pleural endotheliomas cannot be made on the basis of any single criterion. Postoloff's conclusions represent an extension of the concepts of Klemperer and Rabin (41) and of a number of other authors who were impressed by the variegated appearances of endotheliomas of the pleura and who sought a common basis for the manifold differences between individual specimens. The variable histopathologic features of these tumors are not as suggestive of endothelioma as is the characteristic macroscopic appearance of the pleura in the diffuse growth of such a neoplasm.

CLINICAL FEATURES

Age: In common with most other malignant tumors the greatest number of the reported cases occurs between the ages of forty and sixty years. In a series of 192 cases collected from various sources, 6 (3.1 per cent) occurred within the first decade of life; a similar number in the second decade; and 12 cases (6.2 per cent) in the third. Fifty per cent of the cases (96 cases) were noted in patients in the fifth and sixth decades. Smith and Gault (66) report an endo-

theilioma of the pleura in a nine-year-old girl. Manicatide and others observed a similar tumor in an eight-year-old boy; v. Hibler (36) observed an endothelioma of the pleura in a child five years of age; and Goeters (31) reported the case of a two-year-old child with a similar tumor. At the other extreme are the 3 cases of Krumbein (43) and the 4 of Fischer (24), all in patients more than seventy years of age.

Sex: In a collected series of 223 cases, 144 were males and 79 were females, a sex ratio of 1.8 to 1.

Location: Both sides of the chest appear to be equally vulnerable to the disease, although Du Bray and Rosson (19) and Unger (69) have asserted that the right side is more often affected than the left. Addition of the collected series of Fischer (24) and Saccone and Coblenz (59) yields 107 cases in which 56 tumors began on the right side and 51 on the left. In the 7 cases of the present report, 6 were on the right side and one was left-sided in origin.

Symptoms

At the onset of the disease, symptoms may be entirely lacking or minimal. In the early stages of its evolution, endothelioma may produce symptoms which simulate a localized pleuritis. As the disease progresses the patient may complain of localized gnawing pain, asthenia, and a consciousness of some impairment of breathing. Rest and local applications do not relieve the pain nor does local medication alleviate it for more than a short time. Slight or moderate exertion produces dyspnea. There are irregular bouts of elevation in temperature; in the early stages it is low-grade and later it is more elevated but never rising to high levels. In the later stages all symptoms become more aggravated, appetite becomes poor, and there is a rapid loss of weight. In this stage the pain in the chest may be severe enough to mask most of the other symptoms. As the mediastinum becomes encroached upon, the patient may have a persistent cough and may find it difficult to swallow solid foods. In the terminal stages of the disease there is marked dyspnea, orthopnea, diaphoresis, cachexia, and severe pain in the chest which is only partly relieved by large doses of narcotics.

Physical Examination

The physical signs produced by endothelioma of the pleura are dependent upon the stage of the disease at the time the patient is being examined. In the early period there is a paucity of physical signs. As the disease advances, the patient becomes dyspneic, assumes the orthopneic position, and has a tachycardia. Cyanosis is not evident in the early stages of the disease. The temperature may be slightly elevated but rarely is it above 101°F. In the early to moderately advanced stages, the affected hemithorax may be retracted and does not move as well as the contralateral side. Examination of the chest shows impairment to percussion and some suppression of the breath sounds in the region of the tumefaction. As the disease advances still further all the signs become advanced, the dyspnea more marked, the cyanosis prominent, and the chest wall expanded. The intercostal spaces become wider and often tender to pressure. The abnormal physical signs now become pronounced and extend over a greater area of the

thorax. The abdomen, especially on the affected side, becomes prominent. At that stage in the disease when there is a moderate collection of fluid in the pleural cavity, the abnormal physical signs are more diffuse. If the effusion does not completely fill the pleural cavity, rales may be heard in the uncompressed lung tissue. The heart and mediastinum in the early stage remain unaltered in position, but in the later stages they are displaced toward the unaffected side. A pericardial or a pleuropericardial friction rub is not uncommonly heard after all the pleural fluid has been removed. In addition to protrusion of the homolateral abdominal wall, the skin in this area may show a varying degree of anesthesia. Adenopathy is usually absent; only rarely are lymph nodes palpable in the intercostal spaces, cervical region, or axilla on the side of the pleural lesion.

Duration

Geschickter (29) stated that the average duration of symptoms is approximately two years. This is much higher than that observed by other writers, including the present writer. It was Robertson's (57) belief that after the onset of symptoms the patient might be expected to live from a few weeks to a year and, in the very rare instance, a little longer. Analysis of the case records of 46 patients collected from various sources revealed that 37 died within a year; 6 within the first three months after the onset of symptoms; 9 in the following three-month period; and the remaining 22 died in the following six-month period. Of the remaining 9 patients, 5 died within a twelve- to eighteen-month period, 2 in the following six-month period, and the remaining 2 lived, respectively, three and four years after the onset of symptoms.

DIAGNOSIS

Because the clinical picture of endothelioma is frequently not distinctive and the early stages are attended by too few symptoms to indicate neoplastic disease of the pleura, diagnosis is necessarily delayed. The current erroneous conception that, unless the pleural disease is accompanied by an hemorrhagic effusion, the underlying process is not an endothelioma of the pleura has misled the clinician in more than one case. The heretofore stressed futility of therapy, even in the early case of endothelioma, has contributed in no small measure to delay in establishing the diagnosis. Thus, in many proved cases, diagnoses of pleurisy, pulmonary tuberculosis, tuberculous polyserositis, bronchogenic carcinoma, cardiac failure, cirrhosis of the liver, and so forth were entertained until proved otherwise at necropsy. If the possibility of the presence of endothelioma is considered, not only will the physician be rewarded by earlier diagnosis, but he may even be instrumental in eradicating the disease. Every possible means should be employed as early as possible. To this end, detailed roentgenographic studies of the chest, endoscopic studies, pleural fluid cytology examinations, and exploratory thoracotomy should be instituted without delay.

Roentgenographic Studies

In the early stages of pleural endothelioma a solitary opacity may be found in any part of the chest. The lesion may be well circumscribed and have a sharp

or irregular border. As the process advances, the lesion increases in size and may be accompanied by a pleural effusion. There is no characteristic appearance which serves to disclose the true nature of the condition. Occasionally one or more tumor nodules may be seen on the surface of the lung above the fluid level, but more frequently they are not detectable on the conventional roentgenograms. In the later stage, roentgenographic studies of the chest made after the removal of the fluid generally fail to show any remarkable reduction in the opacity of the hemithorax. This should make one highly suspicious of the presence of an endothelioma of the pleura. On the overexposed roentgenogram in the advanced case, one may note an irregular nodular opacity along the surface of the lung. The rapid reaccumulation of the fluid is another clue to the presence of a pleural neoplasm. Roentgenograms taken in a still later stage disclose massive pleural effusion with some displacement of the heart and mediastinum toward the contralateral side. One of the most useful procedures in the roentgenographic diagnosis of endothelioma of the pleura is the induction of a pneumothorax after removal of the fluid. Roentgenograms should be taken immediately after the air is introduced. Overexposed plates taken at this time will usually show tumor nodules on the surface of the pleura.

Endoscopy

Bronchoscopic studies are noncontributory in the diagnosis of pleural endotheliomas. However, pleuroscopy or exploratory thoracoscopy may be of considerable aid in the diagnosis. These procedures will reveal the pleural surface with a mass or masses projecting from the surface of the pleura as well as changes in color and consistency of the pleura. The surface of the neoplastic process has a hemorrhagic appearance and bleeds easily on manipulation. Representative tissue may be removed by thoracoscope for histologic studies.

Aspiration of Pleural Fluid

On introducing a needle into the chest to perform a paracentesis, one is immediately impressed by the resistance of the pleura. This density is not to be expected in early cases nor in those instances in which the tumor process is some distance from the site of the needle puncture. Contrary to the general impression, the fluid need not be frankly bloody. It may be serous or serosanguinous, although in the majority of cases it is quite hemorrhagic. Characteristically, little amelioration of the dyspnea follows removal of the fluid. If any relief should be obtained it is not long lasting, for there is rapid reaccumulation of the fluid. On microscopic examination of the centrifuged fluid, various cells and tumor fragments may be seen. According to Robertson (57), the pleural fluid contains large swollen cells which may be seen as isolated cells or in clumps. The cytoplasm of these cells is characterized by the presence of fat droplets, granules of glycogen, and mucoid globules. The nuclei are vesicular or may show mitotic figures. Lichtenstein (47) found large, round, and polygonal cells in the fluid. Nevertheless, he warns that cytodiagnosis of such fluids is often difficult and sometimes impossible. At times the cells resemble large lymphocytes and

endothelial cells. Not infrequently cells in the pleural fluid which are derived from metastatic carcinoma of the pleura may have many of the characteristics encountered in the cells derived from a primary pleural endothelioma. In addition, both normal mesothelial cells and malignant cells undergo marked changes in pleural fluid and, therefore, interpretation of the microscopic findings is quite unsatisfactory. Mitotic figures alone are not sufficient criteria upon which to base a diagnosis of malignancy because mesothelial cells have the capacity to reproduce in pleural fluid during which process they may show mitosis. It is the composite picture seen under the microscope together with the clinical course which should lead one to suspect the presence of an endothelioma of the pleura.

Exploratory Thoracotomy

In any case in which there is a persistent intrathoracic shadow on the roentgenogram not readily explainable on a satisfactory basis, an exploratory thoracotomy should be performed without procrastination. With the advancement of thoracic surgery and anesthesia, this procedure carries with it minimal hazard.

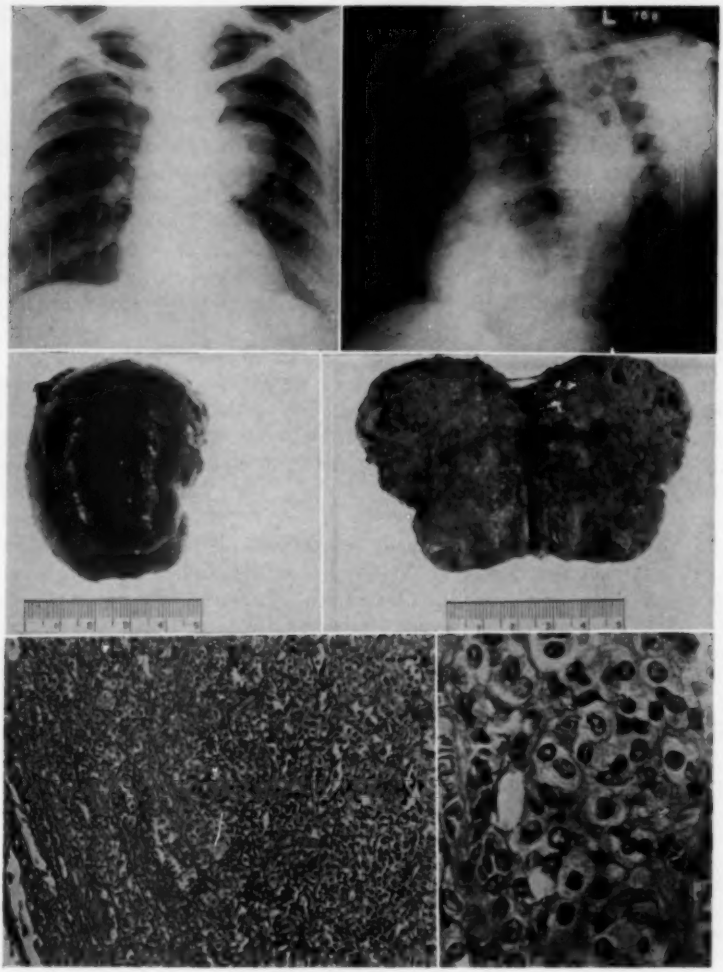
Therapy

Up to the present time, treatment of endothelioma of the pleura has been confined to palliation. Radiation therapy has not diminished the progression of the disease although it has brought about some evanescent improvement. Aspiration of the pleural fluid has helped temporarily to relieve the dyspnea. Nerve block has reduced the pain. All these measures are palliative and do not eradicate the disease. At the present time surgical removal appears to be the only method of attack. However, this cannot be accomplished unless the physician recognizes the condition much earlier than heretofore. It is hoped that improved diagnostic methods will aid in the earlier recognition of these cases. In that event, radical surgical extirpation will be found effective in increasing numbers of cases.

CASE REPORTS

Case 1. J. P., a 54-year-old housewife, first presented herself to a physician approximately three months before entering the Bushwick Hospital. She stated that about five years previously she began to have intermittent dull pains in the left infrascapular region. Two years later the pains became more severe, more prolonged, more persistent, and were not ameliorated by the usual pain-relieving agents. The pains were most severe during inclement weather and whenever she developed an upper respiratory infection. Concomitantly with the change in character of the pain she noted a general lassitude, cough, and some expectoration. In more recent times there had been constant pain in the left infrascapular region and an increase in cough accompanied by mucopurulent expectoration. At times the sputum was blood tinged.

Physical examination revealed a well-developed, apprehensive woman who was not acutely ill. Percussion and auscultation of the right lung revealed no abnormalities. The middle third of the left lung posteriorly was dull to percussion. In this area the breath sounds were somewhat suppressed and had a bronchial character. Roentgenographic examination of the chest disclosed a solitary spherical mass approximately two inches in diameter in the posterior part of the left lung field, suggestive of a benign tumor (figures 1 and 2).



Case 1

FIG. 1. (Upper left) There is a well-circumscribed mass in the left hilar area.

FIG. 2. (Upper right) The left oblique projection shows the tumor to be in the posterior part of the chest.

FIG. 3. (Center left) Tumor removed. The neoplasm is well circumscribed and almost entirely covered by a thin layer of fibrous tissue.

FIG. 4. (Center right) The tumor shown in figure 3 has been cut across. It is semi-solid in consistency and contains several cystlike areas.

FIG. 5. (Lower left) Microscopy (×150) shows groups of polygonal-shaped cells embedded in the fibrous pleura.

FIG. 6. (Lower right) High power magnification (×600) of the cells comprising the tumor.

Operation: The left hemithorax was explored after the subperiosteal removal of the seventh rib posteriorly. In the region of the apex of the lower lobe a reddish-brown circumscribed mass was encountered. The visceral pleura covering the tumor was split proximally. At this point it was noted that the pleura in the region of the tumor was quite thickened and fused with the neoplasm. A plane of cleavage was established between the neoplasm and the pulmonary tissue, and the tumor freed from the substance of the lung. At one point the tumor tissue was fused with the lung tissue, necessitating the removal of a small fringe of adherent lung tissue.

The report of the pathologist was as follows: "The specimen consists of a well-encapsulated tumor measuring 5 by 4 by 4 cm. On its outermost surface there are strands of fibrous tissue. Just deep to this many ecchymotic areas and fine vessels are noted. On section, one notes a solid tumor which is composed of yellowish and hemorrhagic areas with a few dilated reddish patches at the periphery (figures 3 and 4). Microscopic study of the tumor tissue (figures 5 and 6) shows a rather diffuse growth of papillary projections, the outer layer of cells being of a low cuboidal character, with large hyperchromatic nuclei. Within the fibrous stalk there are a number of large irregular cells with multiple hyperchromatic and irregular nuclei. In other sections, diffuse growth of polygonal-shaped cells having a rather pale granular cytoplasm with vesicular nuclei are found. In some areas a number of vascular channels are also present, varying in size from a small capillary-like structure to large blood channels lined by endothelium. In other sections, areas of hyalinization are noted. The histologic picture suggests the probability of blood vessel origin.

Diagnosis: Angioendothelioma of the pleura."

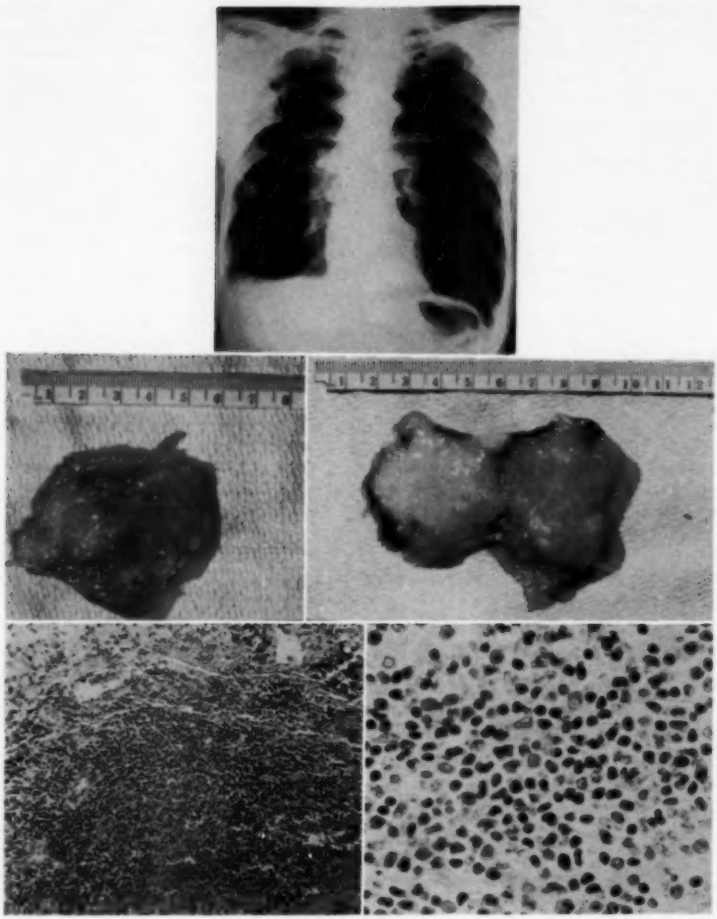
As the wound was being closed, the patient developed ventricular tachycardia and died in spite of all measures to re-establish normal cardiac rhythm.

Case 2. S. G., a 63-year-old painter, was admitted to the Bushwick Hospital on June 9, 1947 because of pain in the chest, fatigue, loss of weight, and a sensation of pressure in the retrosternal region. The onset of these symptoms began a few months before entering the hospital. Except for evidence of recent loss of weight, some venous engorgement on the right side of the neck, and hypotension, the physical examination was essentially negative.

A roentgenographic examination of the chest on June 10, 1947 (figure 7) revealed a lobated mass in the peripheral part of the right lung field opposite the fifth rib posteriorly. A small amount of fluid was present above the right diaphragm and bilateral symmetrical parahilar enlargement of the lymph nodes.

Operation: On June 12, 1947, under local and paravertebral block anesthesia, the chest was explored. The posterolateral parts of the fourth and fifth ribs were resected subperiosteally for a distance of approximately four inches. Immediately deep to the sectioned ribs, a yellowish-gray indurated mass was noted which seemed to be part of the parietal pleura. By means of a circumscribing incision the mass was freed from the chest wall. The growth was then found to be intimately adherent to the underlying lung tissue. The tumor was freed from the pulmonary tissue but in doing so it was necessary to remove the locally adherent lung tissue. The rents in the lung were closed by means of interrupted sutures. The remainder of the wound was then closed in layers. The postoperative course was satisfactory and the patient was discharged from the hospital on June 24, 1947.

The report of the pathologist was as follows: "The specimen (figures 8 and 9) consists of a mass of soft tissue measuring 6 by 4 by 2.5 cm. The external surface is grayish in color and nodular. The cut surfaces are smooth, gray in color, with fine light yellow stippling through which there are bundles of delicate gray streaks. Microscopic examination (figures 10 and 11) shows nests, strands, and sheets of large cells embedded in fibrous connective tissue. The cells vary considerably in size and have scant and occasionally more abundant cytoplasm. The nuclei of the cells are round, oval, or irregular. They are vesicular and some have large nucleoli. Many of the nuclei are in a state of mitotic division. In places the cells are closely packed with little intervening stroma. In other areas delicate strands of tumor



Case 2

FIG. 7. (Top) There is a lobulated mass in the lateral part of the right hemithorax, in the region of the fourth to the sixth posterolateral ribs. A small amount of fluid is present at the base of the right pleural cavity.

FIG. 8. (Center left) Tumor removed. The neoplasm is irregularly nodular on its surface.

FIG. 9. (Center right) The tumor shown in figure 8 has been transected. It is semi-solid, smooth, and glistening on its cut surface.

FIG. 10. (Lower left) Microscopy (×100) shows densely compact cells with deeply staining nuclei.

FIG. 11. (Lower right) High power magnification (×450) of the cells comprising the tumor.

cells alternate with parallel strands of connective tissue. Where the tumor cells are abundant, large areas of necrosis are present. Towards the periphery the connective tissue is traversed by many capillaries containing red blood cells. One surface of the neoplastic process is fringed by a border of lung tissue having narrow alveoli containing red blood cells and clumps of large mononuclear cells laden with rusty brown granules. Clumps of tumor cells are also noted in the air spaces and capillaries of the lung tissue. In other areas the lung tissue is invaded by the tumor cells.

Diagnosis: Endothelioma of the pleura with extension into the lung."

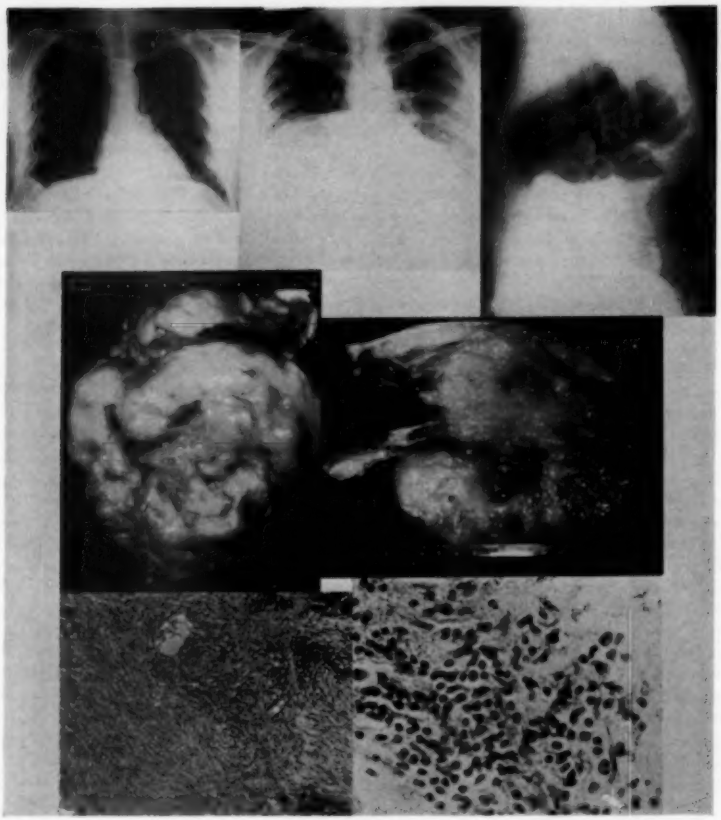
The patient was readmitted to the hospital on April 6, 1948 complaining of dyspnea, cough, some blood-streaked sputum, and loss of weight. A roentgenographic examination of the chest the next day showed an irregularly quadrolateral area of increased density in the region of the previously resected ribs, which extended medially to within an inch of the right hilum. There was some widening of the superior mediastinal shadow. In the lateral projection one noted two rounded nodular masses in the right paratracheal zone. On April 19, 1948 the patient died. Consent for post-mortem examination was not obtained.

Case 3. S. F., a white male, 39 years of age, salesman by occupation, entered Kings County Hospital in October 1947 complaining of pain in the lower part of the right lateral chest wall of approximately three and one-half months' duration. In July of that year the patient sustained a glancing blow to the lower lateral aspect of the right side of the chest from which he never completely recovered. Shortly after the injury he developed a dull, aching pain locally which radiated anteriorly along the course of the seventh rib. The pain was constant, not aggravated by coughing or deep breathing. At that time a diagnosis was made of intercostal neuralgia, and novocaine was injected locally. There was some relief from the pain but this was not long lasting. In the early part of August 1947 the pain became more severe and for the first time a small firm mass was noted in the region of the injury. A roentgenographic study of the chest taken at this time (figure 12) was interpreted as "noncontributory." The symptoms persisted and the mass on the chest wall increased in size. A biopsy of the tumor mass was taken in the latter part of September 1947 and was reported as an "endothelioma."

On October 28, 1947 the patient was admitted to Kings County Hospital. At that time he complained of dyspnea, fatigue, constant pain in the axillary region of the lower right chest, and a growing mass in the lower part of the right chest. Examination at this time revealed minimal limitation of respiratory excursion of the right hemithorax. In the right inferolateral hemithorax, from the anterior to the posterior axillary lines there was a mass measuring about 8 cm. in diameter over which the skin was discolored and red, gray, and blue in color. The swelling was somewhat irregular and firm, but soft in the central region. The tumor mass was fixed to the underlying ribs and not tender to palpation. Roentgenographic studies of the chest at this time (figures 13 and 14) revealed an irregular density at the base of the right hemithorax occupying the lower half of the chest.

Operation: On November 6, 1947, under gas-oxygen-ether anesthesia, the patient was subjected to an exploratory thoracotomy. The tumor mass was seen to originate on the inferior lateral chest wall, extending outward through the chest wall over an area corresponding to approximately five to six ribs and inward to the diaphragm. The lung was uninvolved in the neoplastic process except at the inferior fringe of the right lower lobe. In this region two small deposits were found and removed. The primary tumor mass was dissected free from the diaphragm and the mass removed, together with the five ribs involved in the neoplastic disease (figures 15 and 16). Several neoplastic deposits were found in the mediastinum and on the posterior aspect of the pericardium. Some of these were removed. In order to close the defect in the chest wall, the diaphragm was paralyzed by section of the right phrenic nerve and the muscle sewn to the chest wall. The remainder of the tissues were then closed in layers.

The report of the pathologist was as follows: "The specimen consists of a mass of tissue composed of skin, subcutaneous tissue, and tumor tissue embedded in which are five ribs. The skin is discolored and irregularly firm. The tumor mass is roughly circular measuring



Case 3

FIG. 12. (Upper left) An early roentgenogram of the chest showing an opacity in the right costophrenic sinus.

FIG. 13. (Upper center) Roentgenogram of the chest taken three months later showing an irregular opacity involving the lower half of the right hemithorax.

FIG. 14. (Upper right) The right lateral postion again shows the fluid occupying the lower half of the right hemithorax. Here the fluid is encapsulated anteriorly. In additiion several irregular nodular areas can be seen projecting above the fluid level.

FIG. 15. (Center left) External aspect of the tumor removed. The surface of the neoplasm is irregularly nodular.

FIG. 16. (Center right) The opened specimen shown in figure 15. The tumor contains several cystic areas. Three of the ribs which were removed with the tumor are also shown.

FIG. 17. (Lower left) Photomicrograph of the neoplastic tissue comprising the tumor. There are several nests of small cells embedded in hyaline connective tissue. (×100).

FIG. 18. (Lower right) High power magnification (×450) of the tumor tissue seen in figure 17. The cells are deeply staining, of variable size and have hyperchromatic nuclei.

approximately 15 cm. in diameter. It is of variable color from pale red to yellow. It is irregularly nodular and firm, and in some areas is less dense. Microscopic examination of several sections of tissue shows a malignant neoplastic process of endothelial origin (figures 17 and 18) involving the pleura, ribs, muscle, and subcutis. The pleura is the chief site of the neoplastic disease. Here the component cells are small, ovoid-to-spherical in shape, having hyperchromatic vesicular nuclei and a very small amount of homogeneous eosinophilic cytoplasm. The cells are arranged in sheets around both cellular and hyalinized connective tissue. In other areas the neoplastic cells were arranged around bony trabeculae. There are some areas of osteoid tissue demonstrating the proliferation of bone. In other areas the tumor cells have a perivascular arrangement especially about the blood vessels in muscle.

Diagnosis: Endothelioma of pleura with extension to the chest wall."

The patient was discharged from the hospital on December 12, 1947. His course was satisfactory until about six months later when he developed signs of local recurrence and metastasis to the mediastinum. He died soon thereafter.

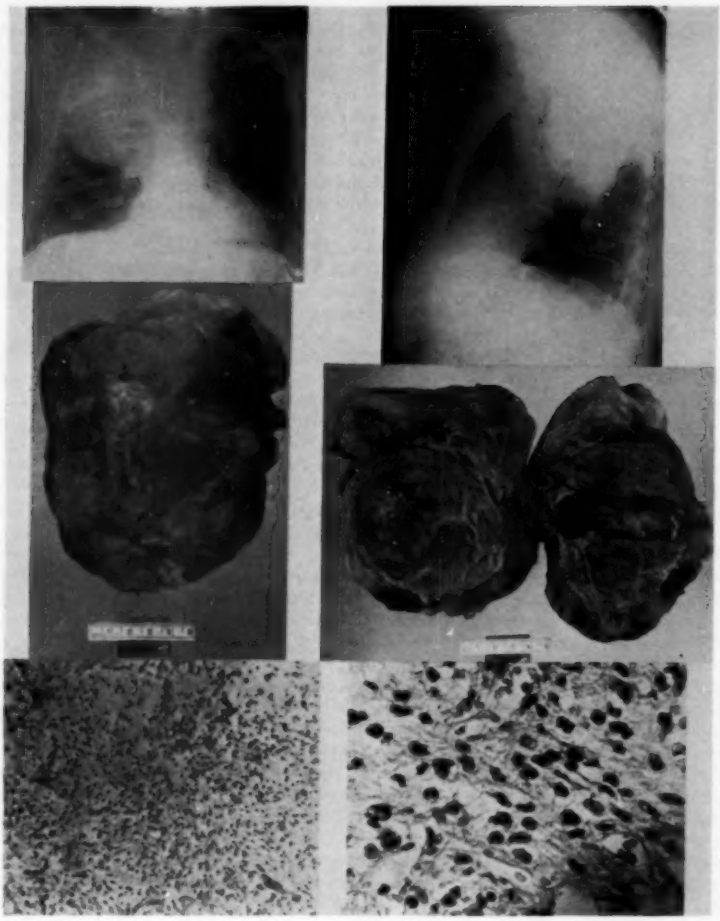
Case 4. D. F., a 63-year-old woman, entered Caledonian Hospital on March 22, 1949 complaining of pains in the right upper abdomen and along the lower part of the right scapula. The pain was not constant, but was becoming more severe in the three weeks prior to admission to the hospital. The exact date of onset was unknown. The physical examination revealed an obese white woman, extremely apprehensive, and complaining of pain in the chest. Dullness to percussion and distant-to-absent breath sounds were noted over the upper two-thirds of the right hemithorax both anteriorly and posteriorly. The abdomen was negative to palpation and percussion. A roentgenographic examination of the chest (figures 19 and 20) showed a large discretely outlined rounded mass in the upper two-thirds of the right thorax, extending from the supraclavicular area down to the eighth posterior intercostal space and from the anterior chest wall to the posterior chest wall. All other laboratory studies, including bronchoscopy, electrocardiogram, blood chemistry, and blood counts, were noncontributory. A diagnosis of intrathoracic tumor was made and on April 6, 1949 an exploratory thoracotomy was performed.

Operation: Upon entering the right pleural cavity a fairly solid mass was encountered compressing the right upper lobe. Upon separating the posterior aspect of the lung from the tumor it was noted that the neoplasm was deep to the visceral pleura. When the visceral pleura was incised outside the tumor area, the neoplasm was readily exposed and separated from the lung and visceral pleura. However, toward the posterior mediastinal area, the tumor and visceral pleura were confluent. The mass was then elevated away from the lung and removed with the fused visceral pleura (figures 21 and 22). As the tumor was delivered, the patient's blood became quite dark in spite of the fact that she was receiving an adequate oxygen supply and had a patent airway. In view of the fact that the blood did not show any improvement in oxygenation, the wound was closed hurriedly and the patient turned onto her back, without any improvement. Suddenly the patient gasped and stopped breathing.

The pathologist's report on the neoplasm was as follows: "The specimen consists of a large ovoid mass measuring 17 by 9 by 8 cm. The external surface is gray-white in color and irregularly lobulated. On section the tumor is glistening gray-white in color. It is semisolid in consistency and rimmed by a zone of gray tissue approximately 3 mm. in depth. This capsular tissue is moderately firm in texture but not scirrhous. The central portion of the neoplasm consists of red-brown, hemorrhagic, soft tissue which contains trabeculae and smooth-walled cavities measuring from 1 mm. to 1.5 cm. in diameter.

On microscopic examination one notes that the tumor tissue is highly cellular. The cells are irregular and ovoid, with moderate variations in size and shape (figures 23 and 24). In focal areas the cells are very irregular and have hyperchromatic nuclei. Multiple sections reveal the origin of the tumor to be in the visceral pleura.

Diagnosis: Pleural endothelioma."



Case 4

FIG. 19. (Upper left) There is a large discrete opacity occupying the upper half of the right hemithorax. The lower border of the mass is concave.

FIG. 20. (Upper right) The tumor seen in figure 19 is shown in the right lateral projection.

FIG. 21. (Center left) Tumor removed. It is semi-solid and covered by a thin layer of fibrous tissue beneath which are many irregular nodular areas.

FIG. 22. (Center right) The opened specimen seen in figure 21. The cut surface is dark and shows a number of trabeculae which separate smooth-walled, cystlike areas.

FIG. 23. (Lower left) The tumor is composed of many round and oval-shaped cells embedded in connective tissue. (×100)

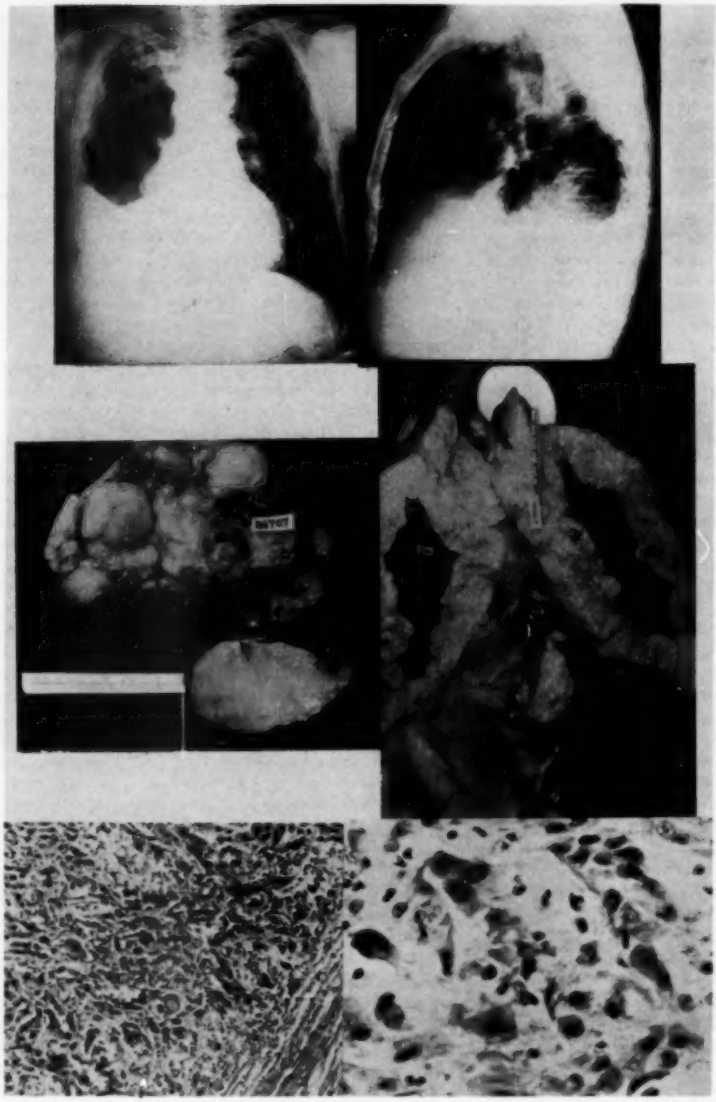
FIG. 24. (Lower right) High power magnification (×600) showing a group of cells seen in figure 23.

Case 5. A. B., a 56-year-old man, entered Kings County Hospital on April 17, 1949, complaining of increasing dyspnea for about six months. During the three months prior to being admitted to the hospital he noticed progressive tightness on the right side of the chest, that he fatigued easily, and that his appetite was becoming poorer although he did not lose any weight. In the two-week period before entering the hospital, all the symptoms became so distressing as to cause complete incapacitation. The physical examination revealed an acutely sick man with limited respiratory motion of the right side of the chest. The percussion note on that side was flat. Auscultation disclosed distant breathing over the greater part of the right hemithorax, with absent breath sounds in the posterior and lateral basilar portions of the right hemithorax. A roentgenographic examination of the chest (figures 25 and 26) disclosed an opacity at the base of the right hemithorax characteristic of encapsulated fluid. In addition, an opacity along the posterolateral chest wall was noted, extending from the third to the sixth ribs. In the region of the sixth and seventh posterior ribs a well-circumscribed mass was present. The remainder of the laboratory findings were noncontributory. The right pleural cavity was aspirated on two occasions, and 2,000 and 2,500 cc. of clear straw-colored fluid were removed. No tumor cells were present in the fluid. On May 17, 1949, an exploratory thoracotomy was performed. On entering the pleural cavity, attention was immediately attracted by the many large nodular areas on the collapsed lung. Further exploration showed similar nodules present on the diaphragm and pericardium. Some of these nodules were about 3 cm. in diameter. So far as could be discerned by palpation, the lung did not contain any tumor masses. In view of the extensive involvement of the tissues it was deemed inadvisable to remove more than a few nodules for biopsy (figure 27).

Necropsy: On September 16, 1949 the patient died. Autopsy disclosed the right pleural cavity completely occupied by dense, firm, nodular tissue. The entire right lung was covered by a thick white, irregular, nodular, dense hull measuring, in some areas, about 3 cm. in thickness. The right lung weighed 4,400 gm. and the left, 450 gm. On cross-section the right lung was found compressed to a small area measuring approximately 3 cm. in diameter (figure 28). The visceral pleura and tumor on the outside of the lung measured approximately 4 cm. in thickness. Tissue similar to that on the surface of the lung extended between the fissures. The lung tissue deep to the pleura as well as all the bronchi and their subdivisions were free of neoplastic tissue, except in one area where the lung tissue and bronchiole were completely enveloped in tumor tissue. Microscopy of the right lung and pleura (figures 29 and 30) revealed a discrete line of demarcation between visceral pleura and lung tissue. The pleura was thickened and fibrotic. Within the pleura there were nests of tumor tissue. The cells comprising the neoplasm were fairly large, mostly polyhedral or flat, the cytoplasm was dark pink, the nuclei were vesicular, hyperchromatic, and irregular.

Diagnosis: Mesothelioma of visceral pleura.

Case 6. J. F., a 54-year-old man, entered the Jewish Hospital in Brooklyn on Feburary 23, 1942 complaining of pain of approximately three month's duration in the lower part of the right side of the thorax. Shortly after the onset of the pain the patient began to experience increasing dyspnea on moderate exertion so that at the time he was admitted to the hospital he was unable to lie flat on his back. During the two months previous to hospital admission he began to experience anorexia, nausea, weakness, and fatigue on mild exertion. Examination at the time the patient entered the hospital revealed an acutely sick man with limited respiratory excursions of the right side of the chest. The percussion note was flat throughout the greater part of the right side of the chest. The breath sounds were absent throughout the entire right hemithorax. To the right of the epigastrium there was a firm mass which was fixed to the underlying structures. A roentgenogram of the chest (figure 31) showed an opacity involving the greater part of the right chest. The remainder of the laboratory findings were noncontributory. Repeated paracenteses disclosed the presence of pink fluid in the right pleural cavity. The fluid did not contain neoplastic cells. On May 17, 1942 the patient died.



Case 5

FIG. 25. (Upper left) There is a collection of fluid at base of the right pleural cavity. In addition there are several nodular areas along the lateral part of the right hemithorax.
FIG. 26. (Upper right) There is a collection of fluid in the lower right hemithorax, the

Necropsy: At the time of the post-mortem examination it was noted that the right lung was encased in an irregular, rubbery, pearl-gray, firm tissue which extended into the interlobar fissures. The left lung weighed 540 gm. and the right lung weighed 2,500 gm. Within the lung in juxtaposition to the pleura, areas of local extensions of the tissue were seen in the pleura (figures 32 and 33). In one area just beneath the pleura, the tumor tissue extended into the wall of a small terminal bronchiole. The other bronchi and their subdivisions were entirely free of any such tissue. The remainder of the pulmonary parenchyma, too, was free of tumor tissue. On microscopic examination of representative pleural tissue (figures 34 and 35) it was found that the masses covering the right lung contained considerable fibrous tissue enclosing larger and smaller groups of cells. These cells were not very large, stained intensely, and varied in size and shape. The nuclei occupied the greater part of the cell substance. The subjacent portions of lung parenchyma presented similar cells. The alveolar spaces were collapsed and contained large mononuclear cells. The cells lining the bronchioles were poorly preserved and did not contain tumor cells.

Diagnosis: Endothelioma of the pleura.

Case 7. W. U., a 33-year-old clerk, had a roentgenogram of his chest taken in March 1939 because of his intimate contact with a person known to have active pulmonary tuberculosis. At that time a circumscribed opacity (figure 36) was discovered in the right infraclavicular area. A roentgenographic study made three months later showed no change. The lesion was interpreted as a healed tuberculous area.

The patient entered the Jewish Hospital of Brooklyn on May 1, 1943, giving a history of increasing fatigue which began in the early part of 1943, frequent upper respiratory infections, and a nonproductive cough for about a year. These symptoms were not remarkably altered until approximately three months before admission to the hospital. At this time his chief complaints were progressive fatigue, cough, dyspnea, anorexia, and loss of weight.

Physical examination revealed an acutely sick, poorly nourished, dyspneic man whose constant reference was to the severe pains on the right side of the chest. The anterior cervical and supraclavicular lymph nodes were enlarged and palpable bilaterally. The trachea was deviated to the left of the midline. There was marked limitation of motion of the right side of the chest, with bulging of the intercostal spaces. The apex beat of the heart was displaced to the left anterior axillary area. The right border of the heart could not be percussed because of the uniform flatness of the right hemithorax. The breath sounds on the right side of the chest were absent. The liver edge was palpable about two inches below the costal margin. Roentgenographic examination of the chest on May 10, 1943 (figure 37) showed an opacity of the greater part of the right hemithorax and some displacement of the heart toward the left. Another film of the chest, made two days later and about six hours after the removal of approximately 3,000 cc. of serosanguinous fluid, failed to show any appreciable change in the opacity in the right hemithorax. Microscopic study of the aspirated fluid showed the presence of many small round cells, large mononuclear cells, red blood cells, and an occasional giant cell. Many large mononuclear cells with irregular deep-staining nuclei were also present. Some of these cells contained more than one nucleus. In some of the cells the nuclei were eccentrically placed. The findings suggested the presence of a malignant tumor.

---

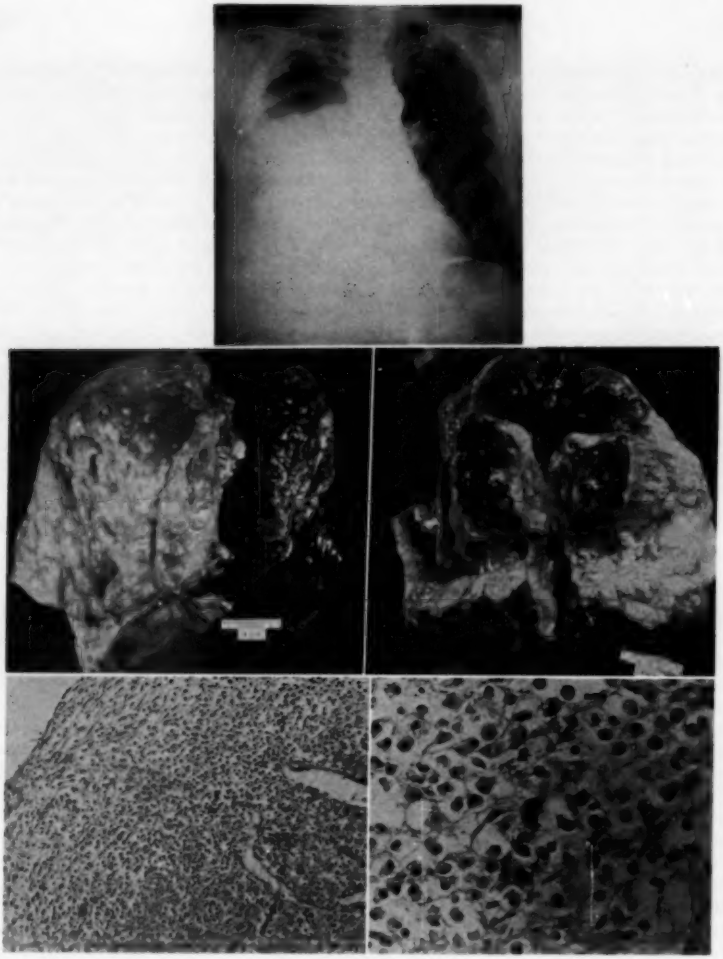
upper surface of which is irregular. In addition, an opacity along the upper posterior part of the chest can be noted.

FIG. 27. (Center left) Specimen of the tumor tissue found on the surface of the lung

FIG. 28. (Center right) Cross-section of right lung removed at the time of autopsy. The dark area represents the compressed right lung. The surrounding pale area is the tumor tissue. The gray area in the lower part of the photograph is adherent diaphragm.

FIG. 29 (Lower left) The tumor is composed of various-sized flat hyperchromatic cells. The pleura is seen in the right lower part of the photomicrograph (×150).

FIG. 30 (Lower right) High power magnification (×600) of the cells comprising the tumor. A nest of large polyhedral, flat, and irregular hyperchromatic tumor cells are shown.



Case 6

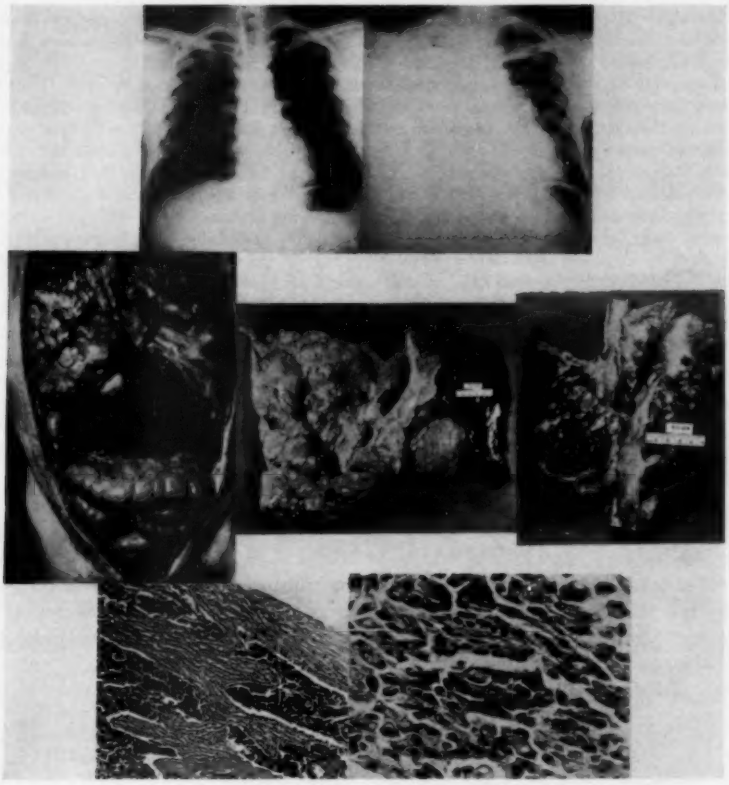
FIG. 31. (Top) Roentgenogram of the chest showing an opacity involving the lower two-thirds of the right side of the chest.

FIG. 31. (Center left) Both lungs as seen at necropsy. The right is covered by a dense nodular mass of tumor tissue most pronounced on the lower two-thirds of the lung.

FIG. 33. (Center right) Part of the surface of the right lung and its tumor covering have been removed. Note the thickness of the pleura and tumor.

FIG. 34. (Lower left) Photomicrograph of the tissue comprising the tumor. The cells are small and enclosed in fibrous tissue (×100).

FIG. 35 (Lower right) High power magnification (×600) of the cells seen in figure 34. The cells vary in size, shape, and staining qualities. The nuclei stain deeply and in many instances occupy an eccentric position.



Case 7

FIG. 36. (Upper left) Roentgenogram of the chest showing a small opacity opposite the tip of the right first rib anteriorly.

FIG. 37. (Upper right) Roentgenogram of the chest taken four years after the one shown in figure 36. There is a complete opacity of the right hemithorax with some displacement of the mediastinum to the left.

FIG. 38. (Center left) Necropsy exposure of the lower thorax and upper abdomen. Note the metastatic involvement of the diaphragm, ribs, and intercostal muscles on the right side.

FIG. 39. (Center middle) The thoracic organs as removed at the time of necropsy. Note the size of the right lung and its covering with tumor tissue.

FIG. 40. (Center right) The right lung has been transected. Note its covering with tumor and the concentration of tumor tissue in the upper part of the lung region.

FIG. 41. (Lower left) Nests of tumor cells within the thickened fibrous pleura. (×150)

FIG. 42. (Lower right) High power magnification (×600) of a nest of tumor cells. The cells are round or ovoid, of variable size, stain deeply, and have hyperchromatic eccentrically placed nuclei.

Necropsy: The patient died about three weeks after admission to the hospital. Necropsy revealed an endothelioma of the right pleura (figures 38, 39, and 40) with metastases to the lung, ribs, intercostal muscles, diaphragm, pericardium, peritoneum, and skin. The right lung was very firm with its external surface covered by a layer of thickened gray visceral pleura measuring up to 0.3 cm. in thickness. On this surface were many nodules measuring approximately 0.5 cm. in thickness and up to 1.5 cm. in diameter. The cut surface of the thickened pleura was gray in color and contained yellow-and-gray—streaked thickened areas. Microscopic study of the neoplastic tissue which covered the right lung (figures 41 and 42) disclosed thickening of the visceral pleura, the composition of which was compactly arranged fibrous tissue within which there were numerous nests and cords of deeply-staining atypical large cells with deeply-staining large nuclei. Occasionally the cells were arranged in sheets. In one place, immediately subjacent to the surface, the cells were loosely arranged. Many of the latter cells were composed of amorphous pink-staining cytoplasm devoid of nuclei.

Diagnosis: Endothelioma of the pleura.

SUMMARY

Endothelioma of the pleura, although a rare disease, is amenable to surgery. It should be thought of in every case of an obscure intrathoracic roentgenographic opacity. Seven cases of this disease are presented, in 4 of which the tumors were removed surgically.

SUMARIO

Endotelioma (Mesotelioma) de la Pleura

El endotelioma pleural, aunque afección rara, es dominable con la cirugía. Hay que tenerlo presente en todo caso oscuro de opacidad intratorácica en la roentgenografía. Preséntanse 7 casos de esta enfermedad, 4 de los cuales fueron tratados quirúrgicamente.

RESUME

Endothéliome (Mésothéliome) de la plèvre

L'endothéliome de la plèvre, qui est une effection rare, peut être opéré. Ce diagnostic doit être envisagé en présence d'une opacité intrathoracique inexpliquée constatée radiologiquement. Sept cas ont été présentés, dont quatre ont été traités chirurgicalement.

REFERENCES

(1) Adler, I.: Remarks on primary endothelioma of lungs and pleura, J. Med. Research, 1901, *6*, 175.

(2) Andral: Precis d'Anatomie Pathologique, Bruxelles, 1837. Cited by Robertson (57).

(3) Aschoff, L.: Path. Anatomie, G. Fisher, Jena, ed. 8, 1936, vol. 2, p. 292.

(4) Banyai, A. L., and Grill, J.: So-called pleuropulmonary endothelioma, Am. Rev. Tubere., 1933, *27*, 193.

(5) Barnard, W. G., and Robb-Smith, A. H. T.: Kettle's Pathology of Tumours, Lewis, London, ed. 3, 1945.

(6) Barrett, N. R., and Elkington, J. St. C.: Two cases of endothelioma of the pleura, Brit. J. Surg., 1938, *26*, 314.

(7) Batne-Jones, S.: Carcinoma of the pleura with hypertrophic osteo-arthropathy, Bull., Johns Hopkins Hosp., 1919, *18*, 213.

(8) Benda, C.: Ueber des primaere Carcinom der Pleura, Deutsche med. Wchnschr., 1897, *23*, 324.
(9) Biggs, H. M.: Endothelioma of the pleura, Proc. New York Path. Soc., 1890, p. 119.
(10) Birch-Hirschfeld: Lehrbuch, Leipzig, 1877, ed. 5, 1896, vol. I, p. 255.
(11) Birnbaum, G. L.: Primary mesothelioma of the pleura, Quart. Bull. Sea View Hosp., 1939, *4*, 462.
(12) Borrmann, R.: Pathologie der Geschwuelste (Sarkon und Endotheliom), Ergebn. d. allg. Path. u. path. Anat., 1900–1901, *7*, 833.
(13) Borst, M.: Die Lehre von den Geschwuelsten, Bergmann, Wiesbaden, 1902, vol. 1, p. 287.
(14) Charcelay: Cited by Robertson.
(15) Clarkson, F. A.: Primary endothelioma of the pleura, Canad. M. A. J., 1914, *4*, 192.
(16) Cornil, L., Audibert, V., Montel, L., and Mosinger, M.: Considerations anatomiques sur le cancer de la plèvre, Bull. Assoc. franc p. l'etude du cancer, 1938, *27*, 51.
(17) D'Alessandro, F.: Considerazioni sui casi di tumori capitati al tavolo anatomico durante cinque anni (1923–1927), Tumori, 1928, *14*, 500.
(18) Doub, H. P., and Jones, H. C.: Endothelioma of the pleura, Radiology, 1942, *39*, 27.
(19) DuBray, E. S., and Rosson, F. B.: Primary mesothelioma of the pleura, Arch. Int. Med., 1920, *26*, 715.
(20) Engelbach: Ein Beitrag zur differential Diagnose pleuritischer Exudate und Neubildungen der Pleura in Anschluss daren ein Fall von Endothelcarcinom der Pleura, Inaug. Diss., Freiburg, 1891.
(21) Ewing, J.: Neoplastic Disease, Saunders, Philadelphia, ed. 4, 1940, pp. 355–359.
(22) Fabris, A.: L'Endotelioma, Tumori, 1930, *16*, 239.
(23) Fahr, T.: Zur Frage des sogennanten Pleuraendothelioms, Virchows Arch. f. path. Anat., 1935, *295*, 502.
(24) Fischer, W., in Henke-Lubarsch: Handb. d. spez. path. Anat. u. Hist, J. Springer, Berlin, 1931, vol. 3, part 3, pp. 558–562.
(25) Fischer-Wasels, B.: Über die primären malignen Geschwulste der Serosadeckzellen, Ztschr. f. Krebsforsch, 1932, *37*, 21.
(26) Fourestier, M., and Duret, M.: Nécessité de la biopsie pleurale pour le diagnostic de l'endotheliome de la plèvre, Presse méd., 1943, *51*, 467.
(27) Fränkel, A.: Über primären Endothelkrebs (Lymphangitis prolifera) der Pleura, Berl. Klin. Wchnschr., 1892, *24*, 497.
(28) Gerundo, M.: Tumors of pleura and peritoneum, J. Kansas M. Soc., 1941, *42*, 18.
(29) Geschickter, C. F.: Mesothelial tumors, Am. J. Cancer, 1936, *26*, 378.
(30) Glockner, A.: Über den sogen: Endothelkrebs der serösen Häute, Ztschr. f. Heilk., 1897, *18*, 209.
(31) Goetjes, W.: Pleuraendotheliom im Kindesalter, Arch. f. Kinderh., 1939, *118*, 92.
(32) Hansemann, D.: Über "Endotheliome", Deutsche med. Wchnschr., 1896, *22*, 52.
(33) Harvey, W. F., Dawson, E. K., and Innes, J. R. M.: Debatable tumors: IX. Endothelioma, Edinburgh M. J., 1940, 47, 513.
(34) Hertwig, O., and Hertwig, R.: Die coelomtheorie: Versuch einer Erklärung des mittieren keimblattes, Jenaische Ztschr. f. Natur., 1881, *8*, 1.
(35) Heuer, G. J.: Surgery of the thorax: Primary malignant tumors of the pleura, in Nelson's *New Loose Leaf Surgery*, Nelson, New York, 1937, vol. IV, pp. 522–530.
(36) v. Hibler: Endothelkrebs der Pleura im Kindersalter, Jahrb. f. Kinderh., 1904, *59*, 367.
(37) Hinsmans, L.: Zur klinischen und pathologisch-anatomischen Diagnose malignen Pleuratumoren, Deutsche med. Wchnschr., 1912, *38*, 1278.
(38) Hochberg, L. A.: Roentgenographic images in primary carcinoma of the lung, Radiology, 1939, *32*, 713.

(39) Hochberg, L. A., Epstein, I. G., and Pernikoff, M.: Endothelioma [mesothelioma] of the pleura, Dis. of Chest, 1947, *13*, 621.
(39a) Kaufmann, E.: Pathology for Students and Practitioners (translated By S. P. Reimann), The Blakiston Company, Philadelphia, 1929.
(40) Keilty, R. A.: Primary endothelioma of the pleura, Am. J. M. Sc., 1917, *153*, 888.
(41) Klemperer, P., and Rabin, C. B.: Primary neoplasms of the pleura, Arch. Path., 1931, *11*, 385.
(42) Klemperer, P., and Tedeschi, C.: Pleural mesothelioma, J. Mt. Sinai Hosp., 1942, *8*, 710.
(43) Krumbein, C.: Über die Natur der Deckzellen der serösen Häute untersucht an Hande eines primären Pleurakarzinoms, Virchows Arch. f. path. Anat., 1924, *249*, 400.
(44) Laennec: Traite de l'auscultation medicale, 1819, vol. II, p. 368.
(45) Leik, D. W.: Carcinoma of the lung: A case which might have been mistaken for endothelioma of the pleura, J. Iowa M. Soc., 1939, *29*, 210.
(46) Ley, R. A.: A propos des tumeurs dites "endotheliomes" de la plevre, Bruxelles-med., 1929, *10*, 57.
(47) Lichtenstein, H.: Die Klinik und Pathologie der primären Pleuratumoren, Deutsche Ztschr. f. Chir., 1931, *233*, 20.
(48) Makey-Rauchberg, cited by Böhm, F., and Sula, L.: Über einen Fall von als Empyem imponierendes Pleuraendotheliom, Beitr. z. Klin. Tuberk., 1939, *92*, 608.
(49) Marras, S.: Sulla istogenesi dei carcinomi indifferenziata della pleura (cosidetti mesoteliomi), Pathologica, 1934, *26*, 8.
(50) Miller, J., and Wynn, W. H.: A malignant tumor arising from the endothelium of the peritoneum, J. Path. & Bact., 1908, *12*, 267.
(51) Montague, E.: Primary endothelioma of the pleura, M. Bull. Vet. Admin., 1932, *9*, 92.
(52) Neelsen, F.: Untersuchungen über den Endothelkrebs (Lymphangitis Carcinomatodes), Deutsch. Arch. f. klin. Med., 1882, *31*, 375.
(53) Patterson, H. S.: A case of endothelioma of the pleura with a review of ninety-six cases, J. M. Soc. New Jersey, 1909, *5*, 373.
(54) Postoloff, A. V.: Mesothelioma of the pleura, Arch. Path., 1944, 37, 286.
(55) Ravenna, E.: Observations anato-pathologiques et cliniques sur les Tumeurs Endothéliales, Arch. de méd. expér. et d'anat. path., 1905, *17*, 325.
(56) Ribbert, H.: Über Pleuratumoren, Virchows Arch. f. path. Anat., 1909, *196*, 341.
(57) Robertson, H. E.: "Endothelioma" of the pleura, J. Cancer Research, 1924, *8*, 317.
(58) Rosenbaum, S.: Beitrag zur Frage der onkologischen Stellung des sogen, Endothelkrekses der Pleura, Ztschr. f. Krebsforsch., 1914, *14*, 543.
(59) Saccone, A., and Coblenz, A.: Endothelioma of the pleura, Am. J. Clin. Path., 1943, *13*, 186.
(60) Sano, M. E., Weiss, E., and Gault, E. S.: Pleural mesothelioma: Further evidence of its histogenesis, J. Thoracic Surg., 1950, *19*, 783.
(61) Scheidegger, S.: Über die sogen, Endotheliome der Pleura, Ztschr. f. Krebsforsch., 1935, *42*, 93.
(62) Schminke, A.: Über Lymphoepitheliale Geschwülste, Beitr. z. path. Anat. u. z. allg. Path., 1921, *68*, 161.
(63) Schulz, R.: Das Endothelkarzinoma, Arch. f. Heilk., 1876, *17*, 1.
(64) Seydel: cited by Zechwer.
(65) Stout, A. P., and Murray, M. R.: Localised pleural mesothelioma, Arch. Path., 1942, *34*, 951.
(66) Smith, L. W., and Gault, E. S.: Essentials of Pathology, ed. 2, Appleton-Century, New York, 1942, pp. 274–284.
(67) Sørensen, E.: Über bösartige Primärgeschwülste des Brustfells, Klin. Wchnschr., 1938, *17*, 571.

(68) Tedeschi, C.: Endoteliomi delle vie Linfatiche Reticuloma del Pulmone, Arch. ital. di anat. e istolog. pat., 1935, *6*, 671.
(69) Unger, R.: Über die Geschwülste der Pleura, Zentralbl. f. d. ges. Tuberk.-Forsch., 1932, *37*, 1.
(70) Vitkus, J. T.: Pleural mesothelioma, Ohio State M. J., 1937, *33*, 1007.
(71) Von Rokitansky: Cited by Robertson (57).
(72) Willis, R. A.: Pathology of Tumors, C. V. Mosby Co., St. Louis, Mo., 1948.
(73) Wintrich, M. A.: Einleitung zur Darstellung der Krankeiten der Respiration organe, Handb. d. spez. Path. u. Therap., 1854, *5*, 377.
(74) Wolff, J.: Die Lehre von der Krebskrankeit von den altesten zeiten bis zur gegenwart, Gustav Fischer, Jena, 1911, *2*, 834.
(75) Wunderlich: Handb. d. Path. u. Therap., 1856, *3*, 494.
(76) Zechwer, I. T.: Mesothelioma of the pleura, Arch. Int. Med., 1924, *34*, 191.
(77) Ziegler, E.: Lehrbuch der Allgemeinen Pathologie und der pathologischen Anatomie für Aerzte und Studirende, Gustav Fischer, Jena, 1898.
(78) Zohlen, J. P.: Endothelioma of the pleura, Wisconsin M. J., 1934, *33*, 202.

BRONCHOGENIC CARCINOMA AS A DIFFERENTIAL DIAGNOSTIC PROBLEM IN PULMONARY DISEASE[1]

I. Carcinoma Arising from Major Bronchi Uncomplicated by Secondary Infection

JOHN H. MOYER AND ALFRED J. ACKERMAN

(Received for publication July 6, 1950)

Bronchogenic carcinoma constitutes a vexing medical problem. The high mortality rate due to this neoplasm has not been reduced significantly despite steady progress in the surgical treatment of intrathoracic diseases. In assessing the various factors responsible for this sad reality, it appears that the therapeutic failures are, at least in part, due to the late recognition of bronchogenic tumors. The insidious character of the disease may cause few, if any, symptoms referable to the respiratory tract. Even when the presence of tumor is suspected, the best diagnostic procedures all too frequently fail in the detection and localization of the underlying pathologic process in its early stage. Furthermore, the protean manifestations of bronchogenic tumors frequently resemble those of other acute or chronic affections of the lung, thus diverting the attention of the diagnostician, with a resultant unwarranted delay of proper therapy. This present report is concerned primarily with focusing attention on the nonspecific character of the clinical symptoms and the roentgenographic changes observed in various phases of the pathogenetic evolution of bronchogenic tumors. At the same time an attempt will be made to correlate the fundamental pulmonary pathology with these same roentgenographic and clinical manifestations.

GENERAL CONSIDERATIONS

Incidence: Once considered a "rare" disease, carcinoma of the lung is now admittedly one of the more common malignant tumors, constituting 6 to 10 per cent of all neoplasms (1, 2, 3). Some writers believe the incidence to be increasing (4), while others attribute the rise in frequency to improved diagnostic acumen (5). The ratio of males to females in reported series varies from 6 to 1 (6) to 3 to 1 (7), respectively. The disease is seen most frequently between the ages of 40 to 60 years, although no age can be said to be immune. The youngest patient in the present study was 22 years of age.

The percentage of operable cases is relatively small, reaching approximately 40 per cent in only a few statistical reports (1); usually it is smaller (8). Five-year survivals are the exception rather than the rule, not exceeding, even in the most optimistic statistics, 8 per cent of the cases (1). A more correct estimate derived from different studies appears to place this survival rate below 5 per cent (8).

Pathogenesis: Although many factors have been incriminated as predisposing to the development of bronchogenic carcinoma, none have been definitely established. Fried (5) denied the existence of any relationship between chronic

[1] From Baylor University College of Medicine, Houston, Texas.

inflammation and bronchogenic carcinoma, despite the fact that he reported 13 cases of carcinoma of the lung occurring in patients with fibrotic pulmonary tuberculosis. Bronchiectasis, although frequently associated with bronchogenic carcinoma, is probably secondary to the bronchial obstruction and resulting infection. The bronchiectasis is almost always distal to the carcinoma and is rarely found at the site of the primary neoplasm. Rubin (9) has suggested that chronic irritation and dusty atmosphere may act as predisposing agents. On the other hand, Vorwald and Karr (10) found that the incidence of carcinoma was not increased in patients with silicosis, nor was there an increase in the incidence of carcinoma in women paralleling their increasing use of tobacco. Coal tar and other carcinogenic agents may be important factors in isolated instances. For example, Frissel and Knox (11) found that the high incidence of bronchogenic carcinoma in the Schneeberg mining district in Germany was due to the radioactivity of the inhaled dust. Mice which have had tar applied to the skin develop primary carcinoma of the lung (12). The neoplastic tendency in mice, which may become 100 per cent cancerous by selective breeding, follows Mendelian recessive characteristics (13). It is extremely unlikely, however, that these agents play any large part in the production of clinical bronchogenic carcinoma in man.

The site of origin of these tumors has likewise been a subject of controversy. The prevailing concept is that all bronchogenic tumors arise from the undifferentiated (indifferent) cells which line the basement layer of the bronchial mucosa. It is from this layer that the mucosa regenerates normally (9). Depending on the degree and type of cell differentiation (14), squamous, adeno-, and anaplastic forms of carcinoma are recognized. The squamous cell carcinoma is the most common and least malignant. Adenocarcinoma, which may consist of mucus-forming cells, is often peripheral in location and metastasizes early. The anaplastic, undifferentiated carcinoma is the most malignant, and is found almost exclusively in males (1). Approximately 75 per cent of all bronchogenic tumors arise from the major bronchi, while 25 per cent arise in the minor peripheral bronchi (9).

Herbut (15) was able to demonstrate by serial sections that in the rare cases of "alveolar cell carcinoma" the tumor also rose from the basal cells of the mucosa lining the smaller bronchioles. If these cells are squamous or anaplastic, they may fill the alveolar spaces similar to inflammatory exudate (carcinomatous pneumonia); or if the cells are cuboidal or columnar, they may line the septa producing an alveolar arrangement.

The pathophysiologic pulmonary manifestations of bronchogenic carcinoma are contingent upon the site of origin of the tumor and the secondary alterations accompanying the disease, which are largely a result of progressive bronchial occlusion. These manifestations are usually an expression of nonspecific complications and in no particular way characteristic of the carcinoma per se. Therefore, for purposes of discussion bronchogenic carcinomas have been divided into three main groups: (*1*) central type or those arising from the main stem bronchi and their divisions; (*2*) central type complicated by secondary infection;

and (3) the peripheral type or those tumors arising from the minor bronchi and bronchioles. The present report is concerned only with tumors of the first group. The other two groups of tumors form the basis of two subsequent reports (16, 17).

BRONCHOGENIC CARCINOMA OF THE MAIN STEM BRONCHI UNCOMPLICATED BY SECONDARY INFECTION

Since central or hilar bronchogenic carcinoma, which originates in a major bronchus, produces symptoms and signs related chiefly to progressive bronchial occlusion if not accompanied by secondary infection, this group is subdivided as follows:

A. Minimal disease without stenosis and without necrosis
B. Partial occlusion
C. Complete bronchial occlusion
D. Peribronchial carcinoma which has ruptured through the bronchus and has spread through the parenchyma; usually varying degrees of bronchial occlusion are also associated with this anatomic type.

Minimal Disease without Occlusion

A carcinoma arising from a major bronchus is initially limited to the mucosa, and produces a thickening of the bronchial wall and roughening of its mucosa at the site of the lesion. As long as this process is limited, there are usually no characteristic clinical symptoms, and routine roentgenographic examinations reveal no abnormalities. If the mucosa becomes eroded, blood streaking may be found, but usually this is a finding of more advanced disease. The most common, and frequently the only, symptom found at this stage is a dry, hacking, cough probably due to mucosal irritation. This is a common symptom in both early and late bronchogenic carcinoma, being reported in as high as 93 per cent of all cases (1).

The criteria on which to base the diagnosis of early carcinoma are elusive and warrant a word of comment. It must be assumed that an early bronchogenic carcinoma is one confined to the bronchial mucosa alone. Nevertheless, the writers, in common with others (8), have had the experience of observing that extensive distant metastases may be present long before the pulmonary lesions cause clinical symptoms or are demonstrable roentgenographically. In fact, the metastases may occasionally give rise to the first clinical symptoms. There is no parallel between the size of the local tumor and the extent of the disease. This is not irrelevant to the prognosis in these cases, since the success of surgical therapy depends much more on the presence or absence of distant metastases than on the state of the local lesion. This point is emphasized because it seems erroneous to assume that a diagnosis of bronchogenic carcinoma before the signs of obstruction and secondary complication set in is necessarily synonymous with the recognition of an early carcinoma.

This is well illustrated by the following case in which no evidence of pulmonary disease was discernible during the entire course of hospitalization, and the tumor

was found on post-mortem examination only after meticulous dissection of the lungs.

Case 1. A 50-year-old white male was in his usual health until six weeks prior to admission, when he received a blow on the neck and back. Following this injury the patient complained of severe backache, low-grade fever, and weight loss. There were no symptoms referable to the respiratory tract. Physical examination was essentially noncontributory except for the production of pain on manipulation of the neck and flexion of the dorsal spine. Laboratory studies revealed only an increased erythrocyte sedimentation rate of 23 mm. per hour.

Roentgenographic examination showed a compression of one cervical and two thoracic vertebrae. There was also a metastatic destructive lesion within the third left rib in the

FIG. 1. *Case 1.* Chest roentgenogram showing no abnormality despite the presence of bronchogenic carcinoma of the left upper lobe bronchus and widespread metastases.

axillary line. The lung fields were clear and the mediastinal nodes were not enlarged. Repeated bronchoscopic examinations were negative. The patient's condition grew progressively worse. He died three months after admission without ever having exhibited clinical signs of the primary neoplasm.

The post-mortem examination revealed a small, anaplastic, nonocclusive, bronchogenic carcinoma in the left upper lobe bronchus. The entire tumor measured approximately 3 mm. in diameter. There were metastases to the lymph nodes of the mediastinum, adrenals, skull, ribs, pelvis, vertebrae, and the long bones of both upper and lower extremities.

This case demonstrates an extreme situation which is an exception rather than a common experience. The more characteristic pattern of pathogenetic evolution finds its expression in progressive bronchial obstruction, causing atelectasis and

secondary complications such as an infection in the peripheral portion of the involved bronchopulmonary segment.

Partial Bronchial Occlusion

The growing tumor may form a mass projecting into the lumen of the bronchus and thus reduce its patency; or it may infiltrate the circumference of the bronchial wall and thus cause a steadily increasing stenosis of the affected bronchus with eventual complete occlusion. At the stage of partial bronchial occlusion, uncomplicated by secondary infection, the clinical symptoms depend usually on two factors: (*1*) necrosis of the mucosal surface of the tumor; and (*2*) the effects of bronchostenosis resulting in decreased aeration. Hemoptysis, seen in 44 to 50 per cent of cases (1, 7) is usually caused by necrosis and ulceration of the tumor mass. It usually consists of blood-streaking of the sputum, but occasionally a massive hemorrhage may occur. In one patient (Case 23) a severe and only episode of hemoptysis caused the patient's death. As long as the neoplasm does not interfere with normal or at least adequate aeration of the involved bronchopulmonary segment, the diagnosis may be very difficult. There may be no symptoms for varying periods of time. A cough or a wheeze, if present, may be confused with symptoms of bronchitis or asthma. The wheeze may be perceived by the patient, but is more frequently elicited only on auscultation by the examiner. If it is localized or unilateral, endobronchial disease should always be suspected. Vinson (19) has been able to find auscultatory evidence of bronchial obstruction, frequently transitory, in 95 to 98 per cent of his cases. Dyspnea may be present with incomplete occlusion, but is usually not severe and becomes clinically manifest only after complete bronchial occlusion and atelectasis have occurred. If dyspnea does occur, it is frequently paroxysmal due to intermittent complete occlusion by bronchial secretions.

Intraluminal nonobstructing carcinomas do not cause the significant roentgenographic alterations detectable on conventional films which may be seen later after complete obstruction and segmental atelectasis have occurred. Instead localized "obstructive" emphysema may be observed. This has been carefully elaborated upon by Westermark (20). More recently Cohen (21) and Rigler and Kelby (22) have again called attention to localized emphysema as a relatively early sign of pulmonary carcinoma. They have emphasized the importance of fluoroscopy or roentgenograms taken during full inspiration and full expiration.

Westermark has divided the effects of this progressive but incomplete bronchial occlusion into three stages. During the first stage the stenosis is only slight. Decreased intra-alveolar pressure results in hyperemia of the pulmonary parenchyma distal to the stenosis, resulting in increased density on the roentgenogram. In the writers' experience this phenomenon is transitory and difficult to observe at best. During the second stage, a more marked constriction of the bronchus results in a valvelike action due to increased flexion and decreased diameter of the bronchus on expiration (8). Excessive air is retained peripherally to the obstruction, causing an emphysema more pronounced on full expiration

than on inspiration. The third stage is characterized by inspiratory and expiratory emphysema. This is a common observation if the patients are seen early and followed carefully. Further constriction of the bronchus induces the fourth stage, complete occlusion and atelectasis. It is not amiss to call attention at this point to the fact that an obstructive emphysema may persist over a long period despite progressive enlargement of the bronchogenic tumor. This obviously must be attributed to a circumferential growth of the tumor which then fails to occlude the affected bronchus completely.

There can be little doubt that localized emphysema when present is a valuable sign of possible partial, segmental, bronchial obstruction. The significance of this finding, however, is most likely contingent upon the development of evidence of progressive obstruction. Circumscribed emphysema alone is certainly not pathognomonic of neoplasm or even partial obstruction, particularly in those cases which exhibit it during both the inspiratory and expiratory phase of respiration. In many instances a circumscribed emphysema cannot be differentiated from pneumatoceles due to causes other than tumor. The value of the distinction is further compromised in those patients with bronchogenic carcinoma who also suffer from the more or less generalized emphysema which is encountered in the same age group. Thus, although localized emphysema is a valuable observation when present, the validity of the sign as an indication of early endobronchial tumor is, in some cases, at least questionable.

The following cases illustrate the above points and emphasize the nonpathognomonic character of localized emphysema:

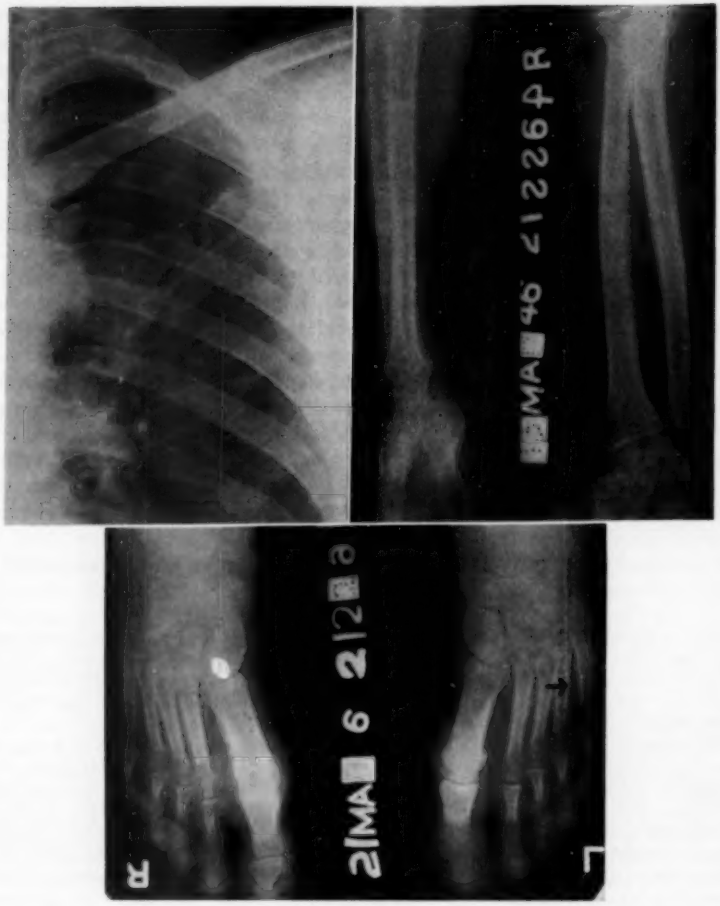
Case 2. A 52-year-old white male was admitted with edema of the extremities, clubbing of the fingers and toes, weakness, weight loss, joint pains, and exertional dyspnea of four months' duration. The erythrocyte sedimentation rate was 54 mm. per hour. The blood proteins were 6.5 gm. per 100 cc. with a normal albumin-globulin ratio. The arterial blood oxygen was 96 per cent saturated.

Roentgenographic examination of the chest revealed a circular shadow of increased density in the left hilar area, somewhat lateral to the descending arch of the aorta. Circumscribed areas of emphysema in the left apex and first intercostal space were present. There was no evidence of significant enlargement of the mediastinal nodes. The diaphragm was mobile. A roentgenographic diagnosis of bronchogenic carcinoma was made. A skeletal survey revealed extensive periosteal reaction along all the bones of the extremities, consistent with "pulmonary osteo-arthropathy." Bronchoscopy failed to demonstrate any evidence of a tumor. An exploratory thoracotomy confirmed the presence of an inoperable bronchogenic carcinoma.

Case 3. A 48-year-old white veteran was admitted because of "asthma" for the past year, an upper respiratory infection, and a cough productive of copious amounts of purulent sputum for two weeks. Physical examination revealed severe respiratory distress with marked generalized wheezing.

Roentgenographic examination of the chest showed a localized emphysema limited to the apex of the left upper lobe. The excursion of the diaphragm was slightly limited, but equal on both sides. The mediastinum was normal. A bronchogram was normal.

Bronchoscopy revealed a "flannel red" mucosa throughout the bronchial tree without evidence of intrabronchial tumor. A diagnosis of purulent bronchitis was made and the patient was treated with penicillin. The symptoms rapidly disappeared and the patient was



Case 2

FIG. 2 (Upper left). Bronchogenic carcinoma present in left hilar area which involved the apical bronchus of the upper lobe. A localized area of inspiratory-expiratory emphysema is present at the left apex.

(Upper right and bottom). Marked periosteal reaction consistent with "generalized pulmonary osteo-arthropathy." All of the long bones were involved. The arterial blood was 96 per cent saturated with oxygen.

discharged two weeks later in good condition. Post-mortem examination six months later, following a traumatic death, revealed localized emphysema of the left apex without evidence of endobronchial disease.

The above case serves to emphasize the occasional nonspecific nature of the roentgenographic signs of bronchostenosis irrespective of the patho-anatomic stage of the obstruction. When the diagnosis is inconclusive in the patient presenting these manifestations, a bronchographic examination may not only demonstrate conclusively the site of the obstruction, but frequently also its cause. Bronchogenic tumors almost invariably show constant filling defects which are usually irregular in outline depending on the gross "surface appearance" of the neoplasm deforming an affected bronchus. The tumor may in some cases encroach upon several bronchial branches. The writers are in agreement with

FIG. 3. *Case 3.* Localized emphysema limited to the apex of the left upper lobe. The roentgenographic changes are very similar to Case 2. No endobronchial tumor was found, thus emphasizing the occasional nonspecific nature of this finding.

Farinas (23) that in cases of incomplete bronchial obstruction, it is necessary to take a series of bronchograms, a procedure which offers the most likely chance for the detection of small alterations of the bronchial tree at a time when no definite parenchymal masses are demonstrable. The bronchostenosis of origin other than tumor usually presents different roentgenographic features. Bronchostenosis due to tuberculosis is not usually limited to a single bronchus and may cause multiple separate stenotic segments in the same bronchus. Diseased bronchi are frequently separated by roentgenographically normal ones. Stenoses of this kind, which are secondary to an inflammatory process, do not produce as irregular defects as bronchogenic tumors. Bronchitis may also account for multiple

stenoses separated from each other, without sharp demarcation, by areas of normal bronchus. Bronchiectasis usually appears as an expansion of the terminal lumen without complete filling of the bronchial branch with the contrast medium. In bronchial asthma a filling of the bronchial tree may be prevented by marked edema and spasm, but no defects within the visualized bronchi are demonstrable.

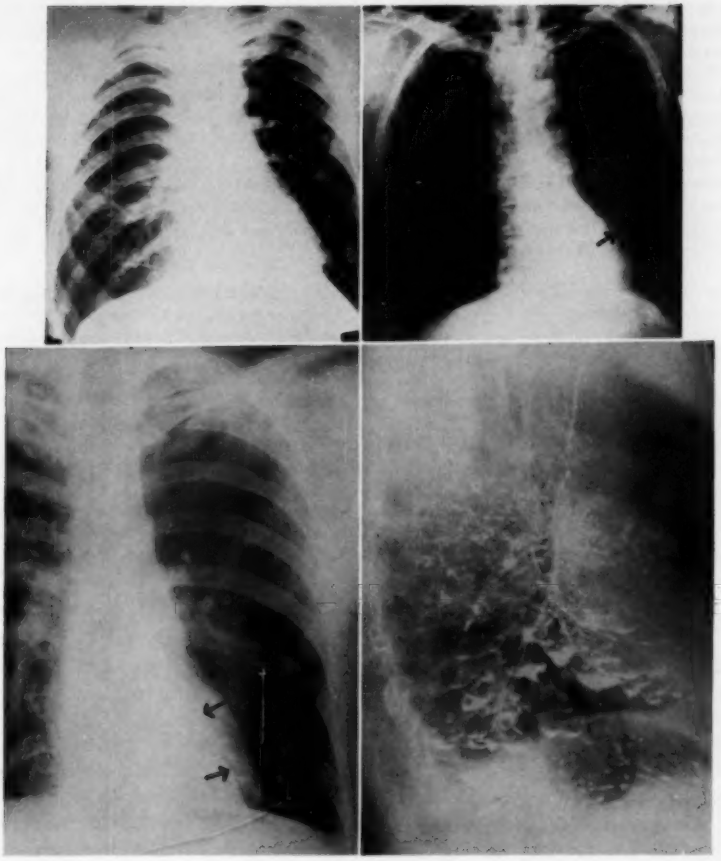
Complete Bronchial Occlusion

Simple uncomplicated atelectasis usually offers no diagnostic difficulty and promptly directs the clinical investigation towards identification of the cause of obstruction. In the writers' experience, dyspnea frequently occurring in paroxysms has been a rather prominent symptom accompanying bronchogenic carcinoma, with complete bronchial occlusion (60 per cent). This was also observed by Edwards (24) in 74 per cent of his cases. In contrast to these findings, Adams (1) noted dyspnea in only the rare instances (1 per cent) unless there was an associated massive pleural effusion. The cause of the dyspnea is not well understood. In 4 patients with dyspnea in the writers' series, the arterial oxygen saturation showed 90 to 97 per cent saturation. The partial pressure of oxygen was not evaluated, however, and it is this factor which is the more important in regulating delivery of oxygen to the tissues. Reflex stimuli arising in the atelectatic area may likewise play an important role. Investigation for endobronchial neoplasms is thus always indicated in atypical asthma, especially in the absence of an allergic background, and particularly if asthma is associated with cough and hemoptysis or appears for the first time past the age of 35 years. The dyspnea may in some instances be extremely severe; and when associated with a history of recent hemoptysis without other preceding symptoms may suggest cardiac failure with or without pulmonary infarction. This symptom complex was observed in one patient who had a pulmonary infarct complicating cardiac failure in addition to a primary bronchogenic carcinoma (Case 17). The possible presence of neoplasm was considered only after hemoptysis persisted, in spite of the fact that good cardiac compensation was obtained by medical management.

The site of the atelectasis, as it is observed roentgenographically, depends on the distribution of the ramifications of the affected bronchus. Because of alveolar collapse of the involved segment due to absorption of air, the lung becomes reduced in volume. This is manifested by a concave border of the lobar margin immediately adjacent to the interlobar pleura. The normal lung becomes emphysematous and the heart and mediastinum are displaced toward the affected side because of its reduced volume. Evaluation of the cause of atelectasis in individual cases depends on supplementary examinations such as bronchoscopy, bronchography, and body-section roentgenography. Tumors, inflammatory diseases, foreign bodies, and occasionally developmental anomalies of the bronchial tree may produce very similar forms of atelectasis.

The following cases exemplify the need for such supplementary examinations whenever a bronchogenic tumor is considered.

Case 4. A 59-year-old white male was admitted because of severe chest pain, hemoptysis, and weight loss of recent origin. He had been complaining of dyspnea and chronic cough



Case 4

FIG. 4 (Upper left). Left lower lobe atelectasis due to bronchogenic carcinoma. Atelectatic lobe margin is poorly visualized behind the heart shadow.

(Upper right). Bucky exposure which better demonstrates the difference in tissue density. The atelectatic left lobe is now easily differentiated.

Case 5

FIG. 5 (Lower left). Bilateral apical fibrotic soft tissue infiltration due to tuberculosis. Left lower lobe atelectasis due to healed endobronchial tuberculosis which apparently caused contraction and occlusion of the bronchial lumen.

(Lower right). Bronchogram showing marked sacular bronchiectasis secondary to the bronchial stenosis.

productive of small amounts of mucoid sputum for the previous ten years. On physical examination of the chest, dullness was noted over the left lower lobe, with decreased breath sounds and a pleural friction rub.

Roentgenographic examination of the chest revealed an atelectatic left lower lobe which was markedly reduced in volume, compensatory emphysema of the upper lobe, and homolateral displacement of the heart and mediastinum. Laminagrams showed obstruction of the main bronchus by a tumor mass in the lumen just distal to the origin of the lower lobe bronchus.

Bronchoscopy revealed a small intramural squamous cell carcinoma occluding the lower lobe bronchus. Examination of the excised tissue after pneumonectomy showed complete occlusion of the left lower lobe bronchus by tumor mass which had also invaded the parenchyma. The lobe was completely atelectatic.

Case 5. A 55-year-old white soldier was studied on routine evaluation prior to overseas shipment. He had no complaints other than a dry cough for six months prior to admission. On physical examination there was some limitation of expansion of the left hemithorax and bronchial breathing at the right apex posteriorly.

Roentgenographic examination of the chest showed bilateral apical fibrotic lesions consistent with chronic pulmonary tuberculosis. The left lower lobe was atelectatic and was considerably reduced in volume. There were a few ringlike, round densities at the base. The upper lobe was emphysematous. Bronchography showed some stenosis of the lower lobe bronchus and numerous saccular bronchiectases within the atelectatic lower lobe and the lingula of the upper lobe.

The cause for the atelectasis and bronchiectases in this case was probably chronic, fibrosed, endobronchial tuberculosis which showed no evidence of recent clinical activity. Sputum studies for tubercle bacilli were positive.

Hilar-type Carcinoma with Peribronchial Extension

Bronchogenic carcinoma may in some instances invade the adjacent pulmonary parenchyma without necessarily causing a bronchial obstruction of significant degree. The resulting unilateral infiltration located in the hilar region is frequently referred to as "hilar type" of primary pulmonary malignancy. Although such hilar opacities may be well circumscribed, they are more commonly diffuse with an indefinite, blurred margin, attributable partly to peribronchial and lymphatic extension of the neoplasm, and partly to lymphatic obstruction.

It has been assumed by some writers (25) that this type of hilar infiltration occurs in the majority of cases of carcinoma, and that it is one of its earliest signs. In the experience of the writers and others (26), unilateral hilar infiltrations are uncommon. By far the most frequent entity has been an intraluminal growth with varying degrees of occlusion and the complications resulting therefrom. As pointed out previously, there are no specific roentgenographic signs of early carcinoma so that no conclusion can be drawn regarding the stage of the disease from the roentgenographic appearance of such tumors. The writers also believe that "hilar infiltrations" are not pathognomonic of bronchogenic tumors arising in this area. Infiltrations of the sort may be observed in other diseases, such as Hodgkin's disease, sarcoidosis, and certain chronic infections, as exemplified by the following cases:

Case 6. A 58-year-old white male was admitted because of intermittent dyspnea for twenty years which had recently become more severe, cough productive of mucoid sputum, pain in

the right chest, and some loss of weight. Physical examination was noncontributory. The erythrocyte sedimentation rate was 20 mm. per hour.

Roentgenographic examination of the chest showed a fairly large, well-circumscribed density in the right hilar area with a few peribronchial extensions into the adjacent parenchyma. The right diaphragm was in the normal position, but showed no motion on fluoroscopy. The findings were interpreted as consistent with the diagnosis of bronchogenic carcinoma.

Bronchoscopy revealed a tumor within the right main stem bronchus, which was identified histologically as a bronchial adenoma. After total pneumonectomy of the right lung, the diagnosis was revised and the tumor was considered to be a malignant adenoma because of multiple lymph node metastases and invasion of the superior pulmonary artery. The patient died three months after surgery from widespread metastases.

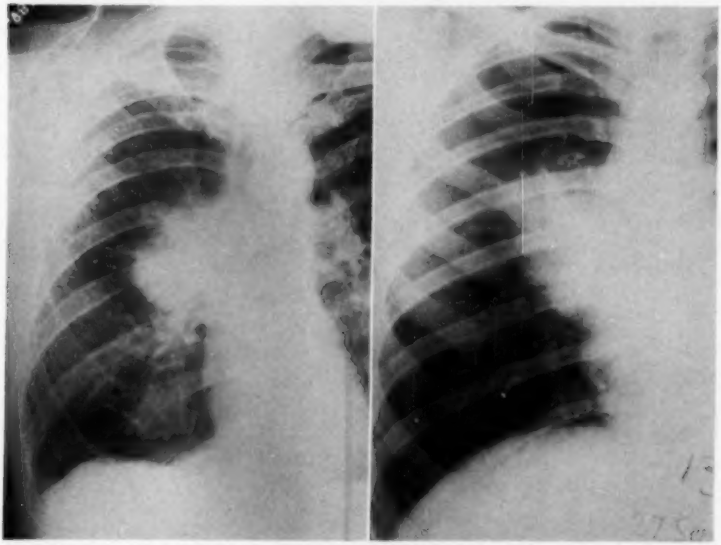


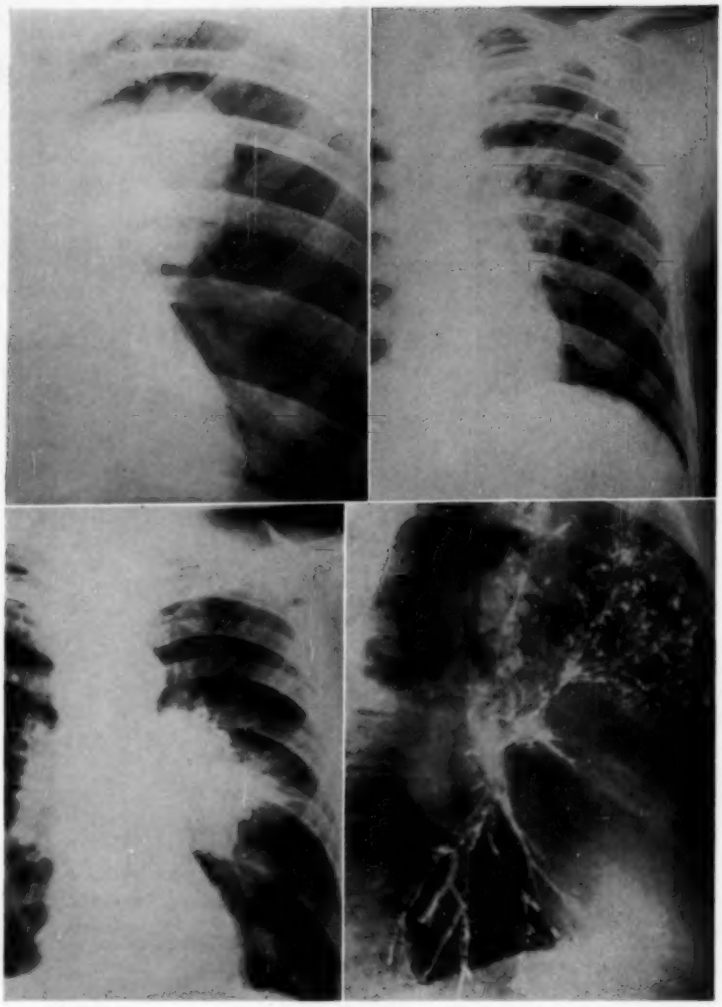
FIG. 6. *Case 6.* (Left) Large, circumscribed hilar mass showing peribronchial extension typical of so called "hilar type" carcinoma. The diagnosis was proved by histologic study.

FIG. 7. *Case 7.* (Right) Hilar infiltration with peribronchical infiltration due to Hodgkin's disease. The roentgenographic findings are very similar to those in Case 6.

Although the differentiation of malignant adenoma from bronchogenic carcinoma may be of oncological interest, the distinction does not appear to be justified from the clinical standpoint.

Case 7. A 39-year-old white male was admitted because of low-grade fever, loss of weight, and weakness of two months' duration. Physical examination disclosed only bilateral axillary adenopathy. The liver and spleen were not enlarged. Laboratory studies were noncontributory.

Roentgenographic examination of the chest showed a rather large density in the right hilum with a somewhat blurred superior and lateral margin, suggestive of peribronchial extension. The diaphragm was freely movable. Examination of material obtained from biopsy of a peripheral node revealed *Hodgkin's disease* of the granulomatous type.



Case 8

FIG. 8 (Upper left). Large left hilar mass with peribronchial infiltrations extending toward the apex. The etiology in this case was sarcoidosis.

(Upper right). Resolution of the left hilar mass seen in figure 8 (upper left) with residual peribronchial and reticular infiltration in the left apex.

Case 9

FIG. 9 (Lower left). Hilar infiltration with radiation into the adjacent parenchyma. The infiltration was unresponsive to antimicrobial therapy. The etiology in this case was localized pulmonary fibrosis apparently following the acute pulmonary infection.

(Lower right). Bronchography showing failure to fill the apical branch of the left lower lobe.

Case 8. A 35-year-old white male was admitted because of cough, chest pain, and enlargement of the cervical nodes of several weeks' duration. Physical examination and laboratory studies were noncontributory.

Roentgenographic examination of the chest showed a large, sharply defined density in the left hilum which was most suggestive of an enlarged lymph node. A sharp distinction between adenopathy alone, however, and a parenchymal tumor was not possible on the basis of conventional roentgenograms.

Two biopsies of peripheral nodes failed to supply evidence of disease. Continued observation showed no significant change in the patient's general condition.

Serial roentgenographic studies showed a progressive "dissolution" of the original mass in the left hilum and a slowly developing peribronchial infiltration in this area which also tended to decrease in size. The right hilar nodes enlarged gradually but did not reach the size of the original mass in the left hilum. These roentgenographic findings were interpreted as consistent with sarcoidosis. The diagnosis was later confirmed by a tonsillar biopsy.

Case 9. A 63-year-old white male was admitted because of cough of several days' duration associated with mucopurulent, blood-tinged sputum and some pain in the left chest. During the past four years he had suffered from recurrent "asthma." Physical examination revealed a temperature of 100°F. There were musical rales throughout both lungs and coarse rales in the left axilla. Laboratory studies showed a total leukocyte count of 14,000 per cu. mm. with 78 per cent neutrophils, 2 per cent eosinophils, and 20 per cent lymphocytes. The erythrocyte sedimentation rate was 28 mm. per hour. Repeated sputum studies for *M. tuberculosis* were negative. A roentgenogram of the chest revealed a large infiltration in the left parahilar area, from which numerous radiations extended into the adjacent parenchyma. Several large calcified parabronchial nodes were present on the right.

On penicillin therapy, the temperature and the leukocyte count fell promptly but the patient showed only slow subjective improvement. The pulmonary infiltration persisted, although it decreased in size. Bronchoscopy failed to disclose definite bronchial disease. Bronchography failed to permit visualization of the apical bronchus of the left lower lobe.

A left lower lobectomy was performed. Examination of resected tissue revealed scattered areas of consolidation and atelectasis. Although the alveolar architecture was well preserved in the periphery, there was a marked proliferation of young fibroblastic elements coursing through the parenchyma and particularly noticeable toward the hilum. The lumina of the bronchi were filled with mucoid secretion but very few inflammatory cells. The pathologic diagnosis was *chronic indurative pneumonia.*

Comment and Summary

Bronchogenic carcinoma constitutes a most challenging differential diagnostic problem in medicine today. Despite recent advances in chest surgery, the prognosis of this disease has not been improved significantly, due in part to the protean manifestations which it presents and a failure of early recognition of these. An attempt has been made here to focus attention on correlation of the pathologic, clinical, and roentgenologic manifestations observed during different phases of the pathogenetic development of these tumors. Special emphasis has been placed on the pulmonary manifestations and differential diagnostic problems presented when this tumor arises from major bronchi and is uncomplicated by secondary infection.

The pulmonary manifestations of bronchogenic carcinomas are for the most part contingent upon the site of origin of these tumors and the complications resulting from progressive bronchial occlusion. The extrapulmonary manifestations are dependent in part upon the pulmonary changes and in part upon the

pathogenicity of the tumor and its tendency towards dissemination. The prognosis is more dependent upon the latter, since the primary lesion may be restricted to the bronchial mucosa and be so small as to present no clinical or roentgenologic pulmonary manifestations; yet the disease may be widely disseminated. Thus, an easily resectable tumor is not necessarily an "early" carcinoma, and vice versa.

Cough is the most common symptom noted in bronchogenic carcinoma. It frequently occurs quite early, before bronchostenosis or mucosal erosion. Hemoptysis in the absence of complicating factors is seen only after erosion of the tumor mass has taken place.

Localized or unilateral wheezing usually represents partial bronchial occlusion. This is frequently accompanied by roentgenographic evidence of localized emphysema distal to the obstruction. However, this finding may also be seen in the absence of bronchostenosis.

Atelectasis becomes manifest after the bronchial lumen has been completely occluded. Although this finding is not specific for carcinoma, it represents endobronchial disease in the majority of instances. In the presence of atelectasis, bronchography and laminagraphy, in addition to bronchoscopy, may be of great aid in reaching a conclusion as to specific etiology.

The "hilar"-type carcinoma with peribronchial radiation is not the most frequently encountered bronchogenic carcinoma. Intraluminal growth with progressive bronchostenosis has been noted much more frequently in the present study. Although the hilar type is quite characteristic when it does occur, similar roentgenographic pictures may be seen in other diseases such as sarcoidosis, Hodgkin's disease, and unresolved pneumonia with resulting fibrosis.

Sumario y Conclusiones

El Carcinoma Broncógeno como Problema de Diagnóstico Diferencial en las Afecciones Pulmonares: I. Carcinoma Originado en los Bronquios Mayores sin Complicación por Infección Secundaria

El carcinoma broncógeno constituye uno de los problemas más agudos de diagnóstico diferencial en la medicina hoy día. A pesar de los recientes adelantos en la cirugía torácica, el pronóstico de esta dolencia no ha mejorado mayor cosa, debido en parte a las manifestaciones proteicas que presenta y a no reconocerse tempranamente las mismas. Trátase aquí de enfocar la atención en la correlación de las manifestaciones patológicas, clínicas y roentgenológicas observadas durante distintas fases del desarrollo patogenético de dichos tumores. Recálcanse en particular las manifestaciones pulmonares y los problemas de diagnóstico diferencial planteados cuando estas neoplasias se asientan en los bronquios mayores y no están complicadas por infección secundaria.

Las manifestaciones pulmonares son, en su mayor parte, contingentes con el sitio de origen de los tumores y con las complicaciones debidas a la oclusión gradual de los bronquios. Las extrapulmonares dependen, en parte, de las alteraciones pulmonares y en parte de la patogenicidad del tumor y de su tendencia a la diseminación. El pronóstico depende más de lo último, dado que la lesión

primaria puede limitarse a la mucosa bronquial y ser tan pequeña que no presente manifestaciones clínicas o roentgenológicas en los pulmones, aun cuando la enfermedad se halle muy difundida. Por eso, carcinoma temprano no representa en modo alguno operabilidad local, lo cual hay que recordar al considerar las alteraciones pulmonares que se manifiesten.

La tos es el síntoma más comúnmente notado en el carcinoma broncógeno, apareciendo con frecuencia bastante tempranamente, antes de la estenosis bronquial o de la erosión de la mucosa. A falta de factores complicantes, la hemoptisis sólo se observa después de tener lugar la erosión de la tumefacción.

El jadeo localizado o unilateral representa por lo general oclusión bronquial parcial, yendo frecuentemente acompañado de signos radiológicos de enfisema localizado, distal a la obstrucción. Sin embargo, puede también observarse este hallazgo en ausencia de broncoestenosis.

La atelectasia se manifiesta después de ocluirse por completo la luz. Si bien este hallazgo no es específico de carcinoma, representa afección endobronquial en la mayoría de los casos. La broncografía y la laminagrafía, unidas a la broncoscopia, pueden resultar de mucho valor aquí para llegar a una conclusión en cuanto a etiología específica.

El carcinoma tipo hiliar con irradiación peribronquial no constituye el cuadro roentgenológico notado más frecuentemente. En el estudio actual observóse mucho más a menudo tumor intraluminal con estenosis bronquial progresiva. Aunque la forma hiliar es bastante característica cuando se halla presente, los estudios roentgenológicos pueden revelar condensaciones indistinguibles en otras dolencias, tales como sarcoidosis, enfermedad de Hodgkin y neumonía irresuelta con fibrosis resultante.

Commentaire et Resumé

(Cancer bronchiogénique. Diagnostic différentiel dans les affections pulmonaires
I. Cancer primitif de la bronche principale non compliqué par
une infection secondaire)

Le cancer bronchiogénique constitue aujourd'hui un des problèmes les plus compliqués du diagnostic différentiel en médecine. En dépit des progrès récents en chirurgie thoracique, le pronostic de cette affection ne s'est pas amélioré de façon appréciable, en raison de ses manifestations protéiformes et l'absence de son identification précoce. Un essai a été tenté dans le but de centrer l'attention sur la corrélation entre les manifestations pathologiques, cliniques et radiologiques observées au cours des différentes phases du développement de ces tumeurs. L'attention est particulièrement attirée sur les manifestations pulmonaires et le problème de diagnostic différentiel qui se présente quand cette tumeur se développe au niveau d'une bronche souche et sans infection secondaire associée.

Les manifestations pulmonaires sont pour la plupart dépendantes du lieu d'origine de ces tumeurs et les complications naissent de l'oblitération bronchique progressive. Les troubles extrapulmonaires sont en partie conditionnés par les manifestations pulmonaires et en partie par la pathogénicité propre de la tumeur

qui tend à la dissémination. Le pronostic dépend surtout de cette tendance, étant donné que la lésion primaire peut être limitée à la muqueuse bronchique et qu'elle peut être si petite qu'elle ne détermine aucun signe pulmonaire clinique ou radiologique; pourtant la dissémination tumorale peut être très étendue. C'est ainsi que le cancer au début n'est pas forcément synonyme d'opérabilité locale. Il faut tenir compte de cette notion quand on prend en considération les altérations pulmonaires présentes.

La toux est un des symptômes les plus communs observés dans le cancer bronchiogénique. Elle se manifeste très précocement, avant la sténose bronchique ou l'érosion de la muqueuse. L'hémoptysie, en l'absence de complications, ne se voit qu'après ulcération de la masse tumorale.

La respiration sifflante localisée ou unilatérale témoigne habituellement d'une occlusion partielle. Ce phénomène s'accompagne souvent de signes radiologiques d'emphysème localisés en un point distal par rapport à l'occlusion. Toutefois, cette manifestation peut également être observée en l'absence de toute sténose bronchique.

L'atélectasie devient manifeste quand la lumière bronchique est complètement obstruée. Ce phénomène n'est toutefois pas une manifestation spécifique du cancer, dans la majorité des cas il représente une affection endobronchique. La bronchiographie et la tomographie, adjointes à la bronchoscopie, peuvent se montrer extrêmement utile dans ces conditions pour établir un diagnostic étiologique.

Le cancer du hile avec extension péribronchique n'est pas très fréquemment visible sur les radiographies. L'extension dans endobronchique avec sténose progressive de la bronche a été observée beaucoup plus souvent au cours de cette étude. Toutefois, ce type hilaire est tout à fait caractéristique quand il existe; des opacités indéfinissables observées au cours des études radiologiques peuvent se voir aussi dans d'autres affections, tel les que la sarcoïdose, la Maladie de Hodgkin, et les séquelles de pneumonie avec lésions fibreuses.

REFERENCES

(1) Adams, R.: Primary lung tumors, J.A.M.A., 1946, *130*, 547.
(2) Fried, B. M.: Bronchogenic carcinoma: A study of 152 autopsied cases, Acta Union Internat. contre Cancer, 1938, *3*, 153.
(3) Graham, E. A.: Primary carcinoma of the lung or bronchus, Ann. Surg., 1936, *103*, 1.
(4) Klotz, M. O.: Primary carcinoma of the lung, Am. J. M. Sc., 1938, *196*, 436.
(5) Fried, B. M.: Bronchogenic carcinoma combined with tuberculosis, Am. J. Cancer, 1935, *23*, 247.
(6) Jones, J. C.: Surgical aspects of bronchogenic carcinoma, J.A.M.A., 1947, *134*, 113.
(7) Olin, H. A., and Elliot, C. A.: Primary bronchogenic carcinoma of the lung, Am. J. Surg., 1941, *54*, 614.
(8) Lindskog, G. E.: Bronchogenic carcinoma, Ann. Surg., 1946, *124*, 667.
(9) Rubin, E. H.: Diseases of the Chest, W. B. Saunders, Philadelphia, 1947.
(10) Vorwald, A. J., and Kahn, J. W.: Pneumoconiosis and pulmonary cancer, Am. J. Path., 1938, *14*, 49
(11) Fribbel, L. F., and Knox, L. C.: Primary carcinoma of the lung, Am. J. Cancer, 1937, *30*, 219.
(12) Jenkinson, E., and Hunter, A.: Bronchogenic carcinoma, J.A.M.A., 1939, *113*, 2392.

(13) Greineder, K.: Das Schichtbild der Lunge, G. Thieme, Leipzig, 1941.
(14) Tuttle, W. C., and Womack, N. A.: Bronchogenic carcinoma: A classification in relation to its treatment and prognosis, J. Thoracic Surg., 1934, *4*, 125.
(15) Herbut, P. A.: Bronchiolar origin of "alveolar cell tumor" of the lung, Am. J. Path., 1944, *20*, 911.
(16) Moyer, J. H., and Ackerman, A. J.: Bronchogenic carcinoma as a differential diagnostic problem in pulmonary disease: II. Carcinoma arising from major bronchi complicated by secondary infection, Am. Rev., Tuberc., 1951 (to be published).
(17) Moyer, J. H., and Ackerman, A. J.: Bronchogenic carcinoma as a differential diagnostic problem in pulmonary disease: III. Peripheral type; carcinoma arising from the minor bronchi and bronchioles, Am. Rev. Tuberc., 1951 (to be published).
(18) Hansson, C. J., and Soderstrom, N.: Celothelioma of the pericardium, Acta radiol., 1943, *24*, 183.
(19) Vinson, P. P.: Primary malignant disease of the tracheobronchial tree: Report of 140 cases, J.A.M.A., 1936, *107*, 258.
(20) Westermark, N.: On bronchostenosis: A roentgenological study, Acta radiol., 1938, *19*, 285.
(21) Cohen, A. G.: Obstructive emphysema and atelectasis in the same lung resulting from bronchogenic carcinoma, J. Thoracic Surg., 1943, *12*, 714.
(22) Rigler, L. G., and Kelby, G. M.: Emphysema, an early roentgen sign of bronchogenic carcinoma, Radiology, 1947, *49*, 578.
(23) Farinas, P. L.: Serial bronchography in the early diagnosis of bronchial carcinoma, Am. J. Roentgenol., 1934, *32*, 757.
(24) Edwards, A. T.: Malignant disease of the lung, J. Thoracic Surg., 1943, *4*, 107.
(25) Olds, V., and Kirklin, B. R.: Primary carcinoma of the lung, Am. J. Roentgenol., 1940, *44*, 357.
(26) Lenk, R.: Roentgendiagnostik der Intrathorakalen Tumoren, Julius Springer, 1929.

HEMOPTYSIS IN CHEST CLINIC PATIENTS[1]

AARON D. CHAVES

(Received for publication July 14, 1950)

INTRODUCTION

Blood spitting is a fairly common complaint among chest clinic patients (1–3). Nevertheless, in this country, there has been no recent appraisal of the significance of this symptom in such patients. Studies of frank hemoptysis as observed in patients selected, for the most part, from hospital material (4, 5) are not representative of the experiences with cases of less extensive bleeding so frequently seen in the average health department chest clinic.

For this reason, a study was undertaken to gather relevant data concerning the occurrence of blood spitting and its association with significant chest disease in patients visiting the free diagnostic service of the Kips Bay Health Center Chest Clinic.[2]

METHODS OF STUDY

Source of Material and Selection of Cases

During the period between January 1, 1948 and December 31, 1949, all patients attending the clinic were carefully questioned about the presence or absence of bloody expectoration. Patients who seemed certain that they had noted expectoration of fresh blood, no matter how slight, not more than three months prior to a clinic visit were selected for study. In 325 cases these criteria were fulfilled.

Within the two-year period of study, 4,771 patients[3] used the diagnostic services of the Kips Bay Chest Clinic. Almost all of the patients were white; about 53 per cent were female, and 89 per cent were over 20 years of age.

Four thousand and ninety-seven patients (86 per cent of the total number) were new clinic cases. These included 121 cases of active pulmonary tuberculosis[4] and 276 cases of inactive pulmonary tuberculosis.[5] The majority of the new clinic patients was composed of persons with minimal respiratory complaints. The clinic attracts very few cardiac patients.

Six hundred seventy-four patients (14 per cent of the total number) were old clinic cases with known pulmonary disease, including 83 cases of active pulmonary tuberculosis[6] and 530 cases of inactive pulmonary tuberculosis.

---

[1] From the Bureau of Tuberculosis, New York Department of Health, 125 Worth Street, New York 13, and the Department of Public Health and Preventive Medicine, Cornell University Medical College.

[2] One of the twenty-one chest clinics of the Bureau of Tuberculosis.

[3] Survey and routine tuberculosis contact examinations excluded.

[4] Includes 8 cases of primary tuberculosis in children and 2 cases of primary pleurisy with effusion.

[5] Includes both arrested and apparently cured cases.

[6] Includes 8 cases of primary tuberculosis in children and one case of primary pleurisy with effusion.

Clinical Investigation

Each case selected for study had the following examinations at the time of the first clinic visit at which the blood spitting was reported: history, physical examination, chest fluoroscopy and roentgenogram, and sputum examination for tubercle bacilli. Additional investigations, such as bronchography or bronchoscopy, were subsequently recommended (as indicated) by the clinic physician. Complete nose and throat examinations were done in only a few instances, each time with negative results. Most of the cases with serious pulmonary diseases were investigated at a hospital where the final diagnosis was established. All patients who were not hospitalized were asked to return to the clinic for re-examination at one- to three-month intervals.

Classification of Cases

On the basis of the clinical findings, as reviewed at the *conclusion* of the study, each case was placed in one of the following three groups:

Group A was composed of cases with thoracic disease which was considered the probable cause of the bleeding.

Group B was composed of cases with significant thoracic disease which was considered as a possible cause of bleeding.

Group C was composed of cases in which there was no clinical evidence of significant thoracic disease.

Group A: Cases with thoracic disease which was considered the probable cause of the bleeding.

In order to avoid confusion, cases with multiple thoracic diseases were listed only according to the most important disease. The criteria of diagnosis for each of the diseases listed in this group are as follows:

Active pulmonary tuberculosis: The criteria of the National Tuberculosis Association (1940) were followed. Bacteriologic confirmation was obtained in all cases.

Bronchiectasis: Bronchograms confirmed the diagnosis in all but 2 cases; in these 2 cases, physical and roentgenographic findings were very suggestive of the diagnosis.

Nonsuppurative pneumonia:[1] Roentgenograms revealed pneumonic lesions which cleared rapidly without leaving any residua.

Bronchogenic carcinoma: This diagnosis was confirmed in all cases by histologic examination.

Suppurative pneumonia and lung abscess: The diagnosis in all cases was established at a hospital. These cases were not secondary to bronchogenic carcinoma or bronchiectasis.

Pulmonary infarction: This diagnosis in each instance was a presumptive one based entirely on clinical impression.

Mitral stenosis: The diagnosis fulfilled the criteria of the New York Heart Association.

Group B: Cases with significant thoracic disease which was considered as a possible cause of bleeding.

Careful observation of all of the cases in this group, with clinic follow-up for at least six months, failed to reveal any other disease which could account

[1] Only cases with frankly bloody sputum are included. Cases with "prune juice" or "rusty" sputum were discarded from the series.

for the blood spitting. The criteria of diagnosis for the diseases listed in this group follow:

Inactive pulmonary tuberculosis: The 1940 criteria of the National Tuberculosis Association were followed. Some of these patients also had pulmonary emphysema of varying degree.

Pulmonary congestion associated with obvious cardiac enlargement: There was roentgenographic evidence of marked cardiac enlargement and definite increase in vascular markings in all cases. All of these patients, on physical examination, showed early signs of cardiac decompensation.

Hypertension was considered present if the systolic pressure was above 150 and the diastolic above 95.

Group C: Cases in which there was no clinical evidence of significant thoracic disease.

All patients in this group had essentially normal lung fields on a conventional chest roentgenogram and normal fluoroscopic findings[3] throughout the period of observation. All roentgenograms were reviewed twice, first by the clinic physician and then by the writer. All patients with a persistent wheeze were thoroughly investigated to exclude the presence of bronchial obstruction. The possibility of overlooking an early carcinoma was constantly in the minds of all of the clinic physicians.

Well-compensated cardiac patients and uncomplicated hypertensive patients were placed in this group.

Fifteen patients from this group, each with either fairly profuse or recurrent bleeding, were subjected to both bronchoscopy and bronchography, with negative results. Two patients with recurrence of bleeding had negative bronchograms but refused to be bronchoscoped. In the remaining patients, there was no recurrence of blood spitting during the period of observation.

The cases in *Group C* were observed at the clinic for the following periods:

41 cases for over six months
52 cases for three to six months
45 cases for one to three months
51 cases attended the clinic but once.

In the 96 cases with a follow-up period of less than three months, correspondence with the patient or referring physician five to six months following lapse of clinic visits was successful in eliciting follow-up information in 87 instances. In all of these cases, the information obtained indicated that the patient was in apparent good health and had suffered no recurrence of blood spitting.

OBSERVATIONS

Three hundred twenty-five patients, or 6.8 per cent of the total number visiting the clinic during the period of study, complained of recent blood spitting. The distribution of these cases according to clinical groups, age, and sex is noted in table 1.

Over 90 per cent of the patients were white. Almost 90 per cent of the patients

[3] This included inspection of the lung fields in both oblique views, anteroposterior view, and during both inspiration and expiration.

with significant chest disease as the probable cause of the blood spitting (*Group A*) were over 40 years of age, and among these over 70 per cent were males. No significant seasonal incidence was noted.

Relationship of Character of Blood Spitting to Clinical Findings

Because of the difficulty in obtaining accurate accounts of the amount and type of blood expectorated in most instances, a careful study of the relationship between the character of the blood spitting and the clinical findings could not be made. In general, there was a high degree of correlation between severity of bleeding and severity of pulmonary disease. Nevertheless, exceptions to this

TABLE 1

Distribution by Age and Sex of 325 Cases of Hemoptysis Arranged in Three Clinical Groups

Clinical Group	All Ages		Under 20		20 to 40		Over 40		Combined Total	
	Male	Female	Male	Female	Male	Female	Male	Female	Number	Per Cent
Total.....	175	150	12	17	64	83	99	50	325	100
Group A Thoracic disease found; probable cause of hemoptysis	65	26	2	0	9	10	54	16	91	27.7
Group B Thoracic disease found; possible cause of hemoptysis	29	16	1	0	7	2	21	14	45	13.8
Group C No clinical evidence of significant thoracic disease	81	108	9	17	48	71	24	20	189	58.5

general trend were sufficiently frequent to indicate the unreliability of the character of blood spitting as an index of severity of underlying disease. In several of the cases with serious pulmonary disease it was the slightest degree of blood streaking which brought the patient to the clinic. On the other hand, 10 patients, all intensively investigated and carefully followed, had fairly profuse bleeding with no demonstrable thoracic disease or discernible source of the bleeding.

Analysis of Findings by Clinical Group

Group A. Significant thoracic disease considered the probable cause of blood spitting: Ninety-one cases, or 27.7 per cent of the series, met the criteria for placement in this group. In table 2 may be seen the pulmonary diseases in this group in order of frequency and listed by age, group, and sex.

In 38 patients, or 41.7 per cent of the group, the hemoptysis was due to active pulmonary tuberculosis. Seven of these patients were experiencing a reactivation of previously diagnosed arrested disease at the time of the hemoptysis.

There were 17 cases of bronchiectasis of which 7 were previously known to the clinic. Most of the cases were of the dry variety with minimal-to-moderate cylindrical dilatation. Two of the 17 patients had acute pneumonitis during observation, and 9 had evidence of inactive pulmonary tuberculosis in addition to the bronchiectasis.

Thirteen patients had nonsuppurative pneumonia. This figure probably represents a minimal number with this disease as, undoubtedly, many cases with primary atypical pneumonia came to the clinic after the pneumonic lesions had cleared.

TABLE 2

Group A

Thoracic Diseases Adjudged Responsible for Hemoptysis in 91 Patients by Age and Sex

DIAGNOSIS	UNDER 20		20 TO 40		OVER 40		TOTAL	
	Male	Female	Male	Female	Male	Female	Number	Per Cent
Total	1	0	10	9	55	16	91	100.0
Active pulmonary tuberculosis	0	0	7	6	22	3	38	41.7
Bronchiectasis	0	0	1	1	9	6	17	18.7
Nonsuppurative pneumonia	1	0	1	2	9	0	13	14.3
Bronchogenic carcinoma	0	0	0	0	7	0	7	7.7
Suppurative pneumonia and lung abscess	0	0	1	0	4	1	6	6.6
Pulmonary infarction	0	0	0	0	2	3	5	5.5
Mitral stenosis	0	0	0	0	2	3	5	5.5

There were 7 cases of primary bronchogenic carcinoma and in only one of these was the tumor sufficiently localized to permit surgical resection.

Six patients had suppurative lung disease; 2 with acute and 2 with chronic lung abscesses. Two other patients had suppurative pneumonia.

Five patients were suspected of having had pulmonary infarctions. The episodes were associated with cardiac decompensation in 3 patients, occurred soon after an appendectomy in one, and were probably a complication of thrombophlebitis in an additional patient. Mitral stenosis with insufficiency, which was well compensated, was the sole finding to which to attribute the hemoptysis in 5 patients.

It is of particular interest that in all but 2 of the 91 cases in *Group A* there were significant abnormal roentgenographic or fluoroscopic findings in the chest at the time the blood spitting was first reported.

In the 2 patients whose initial chest roentgenograms and fluoroscopic findings were normal, subsequent examinations indicated that one (with a persistent unilateral wheeze) had a bronchogenic carcinoma and the other, pulmonary infarction secondary to thrombophlebitis. In both instances, the history and physical findings were so suggestive of the ultimate diagnosis that prompt hospitalization was urged at the time of the first clinic visit, in spite of the normal chest roentgenogram and fluoroscopy.

Group B. Significant thoracic disease, possibly the cause of the blood spitting: Forty-five patients, or 13.8 per cent of the series, were in this group with significant thoracic disease which was a possible cause of hemoptysis. Thirty-one patients were found to have pulmonary tuberculosis which was presumably inactive. As bronchograms were not done in any of these cases, some instances of bronchiectasis may have been overlooked. Obvious cardiac enlargement not due to mitral valvular disease was present in 13 patients. Ten of these had hypertension, and some degree of cardiac decompensation was present in all.

Group C. No clinical evidence of significant thoracic disease: One hundred eighty-nine cases, or 58.5 per cent of the series, fulfilled the criteria for inclusion in this group. Many of these patients complained of spitting up very small amounts of blood, in many instances only a few streaks on one or two occasions. The source of bleeding was not found in any of these cases, although it was suspected that in an appreciable number the bleeding originated from the gums, nasal passages, sinuses, pharynx, or larynx.

Many of the patients had had acute respiratory diseases, some of which, undoubtedly, had represented some type of bronchopneumonia which had cleared by the time of clinic admission. In several of the cases signs and symptoms suggestive of acute bronchitis were present. A few patients had chronic bronchitis, usually with emphysema. There were a small number of patients with well-compensated cardiac disease (other than the 5 with mitral stenosis and insufficiency) and 6 patients with hypertension unassociated with obvious cardiac enlargement. Again, there may have been some cases of bronchiectasis in this group, detectable only by bronchography; if so, the bronchiectasis was probably not extensive or important. The possibility that adenoma, broncholithiasis, or other infrequent causes of hemoptysis were present in some of these cases seemed remote, but, of course, was not definitely excluded.

COMMENTS

The various causes of pulmonary bleeding and the necessity for prompt investigation whenever this phenomenon occurs have been very adequately discussed in recent articles (1–5). It is worth while, however, to mention some practical aspects concerning the management of the large number of cases with blood spitting which are encountered in the average health department chest clinic. It is generally conceded that every person who complains of blood spitting, no matter how slight, should have a careful history, physical examination, and chest roentgenogram preferably supplemented by fluoroscopy. But it is obviously impossible to subject all such patients to bronchoscopy, bronchography, complete nose and throat examinations, and complete bacteriologic studies even

at the few clinics which can readily offer such facilities. Nor is it always possible or psychologically sound to have such patients remain under clinic supervision indefinitely. Thus, it is necessary to employ "rules of thumb" to separate the significant from the insignificant cases of blood spitting, so that the former may be immediately subjected to definitive investigation and the latter, reassured without too much delay. In all instances, the danger of overlooking a small bronchogenic carcinoma must be given serious, but also practical, consideration.

While the type and amount of bleeding are not reliable indices of the seriousness of the underlying disease, there is no question concerning the need for exhaustive studies in all cases with massive or recurrent bleeding, even in the presence of a normal chest roentgenogram and physical examination. It should also be emphasized again that in any patient with blood spitting the presence of persistent additional symptoms or abnormal chest findings, either on physical examination or roentgenogram and fluoroscopy, calls for the prompt institution of all studies necessary to establish a precise diagnosis.

Nevertheless, the problem still remains of what additional investigations, if any, should be carried out in the large number of otherwise apparently healthy persons with *blood spitting of minimal extent* in whom *fluoroscopic*, *roentgenographic*, and *physical* examinations reveal no pertinent abnormalities. One gains the impression, from the results of the analysis presented above, that there is little likelihood of life-threatening pulmonary disease being present in the overwhelming majority of such cases, particularly in those under forty years of age. It would seem reasonably safe to reassure such patients, with the advice that they consult the clinic or a physician promptly if bleeding recurs or if new respiratory complaints develop. As an added precaution, such patients, when seen at the Kips Bay Chest Clinic, are asked to submit sputum specimens for examination for tubercle bacilli and, if over forty, for tumor cells as well.

SUMMARY

1. Among 4,771 patients who attended the Kips Bay Chest Clinic from January 1, 1948 to December 31, 1949, 325, or 6.8 per cent of the total, complained of recent blood spitting.

2. Significant thoracic disease, which probably caused the blood spitting, was found in 91 cases, or 27.7 per cent of the series (*Group A*).

3. Significant thoracic disease, not necessarily related to the blood spitting, was found in 44 cases, or 13.8 per cent of the series (*Group B*).

4. No clinical evidence of significant thoracic disease was present in 189 cases, or 58.5 per cent of the series (*Group C*).

SUMARIO

La Expectoración de Sangre en los Enfermos de la Clínica Torácica

1. Entre 4,771 enfermos que asistieron a la Clínica Torácica de Kips Bay del 1° de enero de 1948 al 31 de diciembre de 1949, 325, o sea 6.8 por ciento del total, se quejaron de hemoptisis recientes.

2. En 91 casos, o sea 27.7 por ciento de la serie (Grupo A), se descubrió enfermedad torácica de importancia, que probablemente ocasionaba la hemoptisis.

3. En 44 casos, o sea 13.8 por ciento de la serie (Grupo B), se descubrió enfermedad torácica de importancia, pero no forzosamente relacionada con la hemoptisis.

4. En 189 casos, o sea 58.5 por ciento de la serie (Grupo C), no había signos clínicos de enfermedad torácica de importancia.

RESUME

Le crachement de sang chez les malades d'une Clinique des affections thoraciques

1. Sur 4.771 malades qui se sont présentés à la clinique des affections thoraciques de Kips Bay du ler janvier au 31 décembre 1949, 325 d'entre eux, soit 6, 8 pour cent, se sont plaints de crachements de sang.

2. La présence d'une affection thoracique confirmée, comme la cause probable du crachement de sang, a été constatée dans 91 cas, soit 27,7 pour cent de la série (Groupe A).

3. La présence d'une affection thoracique, qui n'était pas nécessairement liée au crachement de sang, a été constatée dans 44 cas, soit 13,8 pour cent de la série (Groupe B).

4. Aucun signe clinique d'affection thoracique n'a été mis en évidence dans 189 cas, soit 58 pour cent de la série (Groupe C).

Acknowledgment

The writer wishes to express his deepest gratitude to the many excellent physicians who fortunately were assigned to the Kips Bay Chest Clinic during the period of this study and without whose interest and endeavor this report would not have been possible.

REFERENCES

(1) Franklin, L. M.: A note on haemoptysis: Some figures from a tuberculosis dispensary, Tubercle, 1945, *26*, 28.

(2) Heller, R.: The significance of haemoptysis, Tubercle, 1946, *27*, 70.

(3) Mann, B.: A clinical survey of bronchiectasis, Tubercle, 1949, *30*, 254.

(4) Jackson, C. L., and Diamond, S.: Hemorrhage from the trachea, bronchi and lungs of nontuberculous origin, Am. Rev. Tuberc., 1942, *46*, 126.

(5) Abbott, O. A.: The clinical significance of pulmonary hemorrhage: A study of 1316 patients with chest disease, Dis. of Chest, 1940, *14*, 824.

A CLINICAL, FUNCTIONAL, AND NEEDLE BIOPSY STUDY OF THE LIVER IN PULMONARY TUBERCULOSIS[1]

MARVIN SEIFE, BRUCE J. KESSLER, JOSEPH HOFFMAN, AND JAMES R. LISA[2]

(Received for publication July 17, 1950)

INTRODUCTION

The present communication is the report of the clinical, functional, and histologic investigation by needle biopsy of the liver in 70 cases of chronic active pulmonary tuberculosis. Hepatic lesions of various types, both tuberculous and nontuberculous, were present in a high percentage of the group. Subnormal cholesterol levels were more closely parallel to the clinical course of the disease than any other functional test.

The clinical diagnosis of tuberculosis of the liver is rarely made with certainty. In patients with known pulmonary tuberculosis, jaundice and hepatomegaly in association with chills and fever are held to be very suggestive of miliary involvement (1, 2).

Pathologic studies have dealt largely with autopsy material composed of fatal cases of chronic pulmonary, intestinal, or miliary tuberculosis. Saphir (3), in 100 consecutive cases of pulmonary tuberculosis, found tubercle formation in the liver in 80 instances. Other investigators (4, 5, 6) have reported the incidence of hepatic lesions to range from 63 to 99 per cent of patients with tuberculosis in other organs. Bile duct tuberculosis, massive caseous tuberculosis, and tuberculous abscess have also been reported, as well as focal necroses (1). Fatty metamorphosis of the liver has been a common finding in patients with tuberculosis. Saphir (3) found it in 34 per cent of his series. In 581 autopsies in cases of pulmonary tuberculosis, Jones and Peck (7) found that 41.9 per cent displayed fatty changes, and Ullom (4) found 35 per cent.

Ante-mortem histologic studies of hepatic tissue obtained by needle biopsy have been carried out only in recent years. Janbon, Cazal, and Bertrand (8) performed 45 biopsies in 24 patients with miliary tuberculosis. They classified their findings into three groups: specific tuberculous lesions, nonspecific inflammatory and epithelioid lesions, and fatty changes. They likewise described hyalinization and scarring of hepatic lesions following treatment with streptomycin. Craddock and Meredith (9) reported one case of miliary tuberculosis diagnosed by needle biopsy examination of tissue obtained.

The hepatic function of patients with tuberculosis has been extensively studied. Elevated globulin and decreased albumin concentrations have been consistently found (10, 11, 12). Low values for total serum cholesterol (10, 11, 13), bromsulfalein retention (14), and prothrombin have been reported (15, 16) as well as abnormalities in cincophen oxidation, galactose tolerance, and the icterus index

[1] From the First and Second Medical Divisions and the Laboratory of Pathology, City Hospital, Welfare Island, Department of Hospitals, New York 17, N. Y.

[2] With the technical assistance of Frank Scudero and Alida J. Ruiz.

(17). All of these tests have been stated to parallel the course of pulmonary tuberculosis. The results of determinations of the total serum protein concentrations have been inconsistent, as normal (15), increased (10), and decreased values (11) have been found by different investigators.

MATERIALS AND METHODS

Seventy unselected cases of pulmonary tuberculosis, diagnosed by roentgenographic and bacteriologic means, with lesions ranging from minimal to far advanced in extent, were chosen for study. The investigation included history, physical examination, a group of liver function tests, and microscopic examination of tissue obtained by liver biopsy. The tests of function included the thymol turbidity (18), determinations of the serum bilirubin (19, 20), serum cholesterol and cholesterol fraction (21), serum protein and albumin-globulin ratio (22), serum alkaline phosphatase (23), prothrombin time (24), and the 45-minute bromsulfalein retention test, in which 5 mg. per kg. of body weight were used. Biopsy was performed with the Vim-Silverman needle, using the intercostal approach. The specimens were fixed in 10 per cent formalin solution and stained with hematoxylin and eosin. The length of hospital stay at the time of biopsy ranged from 1 to 356 days. Biopsy and the tests of function were done within a few days to a few weeks of each other.

TABLE 1

Incidence and Type of Hepatic Lesions in 70 Patients with Pulmonary Tuberculosis*

Tubercle	9
Focal caseation necrosis	9
Focal necrosis—acute	50
subacute	12
Fatty metamorphosis	14
Cirrhosis	13
Periportal inflammation	14
Nuclear glycogen deposits	3
Increased intracellular bile	1

* More than one type of lesion present in most cases.

At the time of the study, the patients were receiving a 3,400 caloric diet with multivitamin supplements. Many were receiving streptomycin and para-aminosalicylic acid. All were on complete or modified bed rest.

OBSERVATIONS

Pathology

The pathologic changes found in the livers of the 70 patients can be divided into two large groups, tuberculous and nontuberculous, with most of the cases having more than one type of lesion. The incidence of the various types of lesion found may be seen in table 1.

The *distinct tubercles* were chiefly epithelioid in nature with central caseation, and were frequently associated with a marked eosinophilic component and a peripheral collar of lymphocytes. Giant cells were very infrequent. In one case in which a nest of tubercles was present, a small focus of acute infarction was adjacent to the tuberculous area. Seven of the lesions were intralobular and two were periductal.

Focal caseous lesions, highly suggestive of acute tuberculosis, were characterized by degenerating nests of hepatic, polymorphonuclear, and lymphocytic cells. They were all intralobular and one was perivascular, surrounding the central vein.

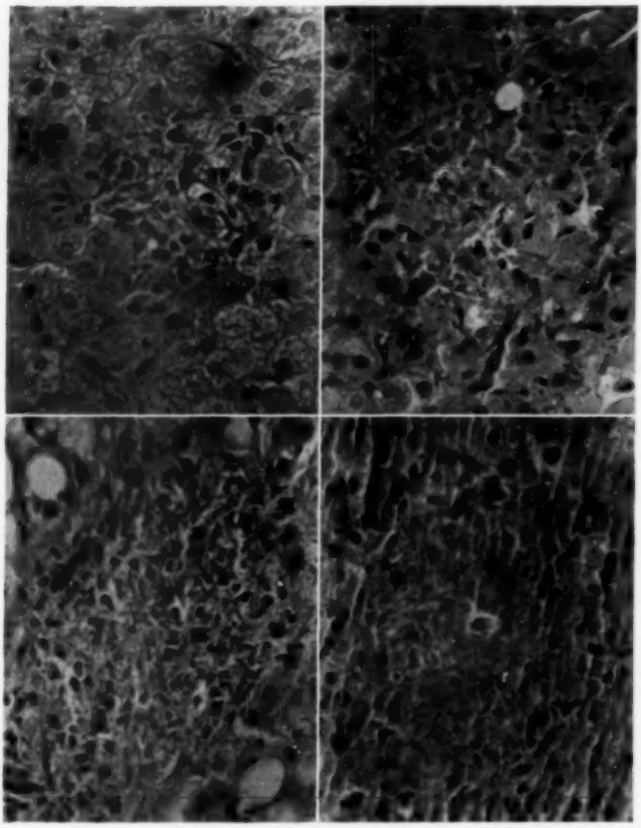


FIG. 1. (Upper left) Acute minute intralobular focal necrosis
FIG. 2. (Upper right) Intralobular acute focal necrosis
FIG. 3. (Lower left) Larger intralobular focal necrosis suggestive of early caseation necrosis.
FIG. 4. (Lower right) Centrolobular focal necrosis surrounding the central vein

The *acute focal necroses* were minute, ill-circumscribed lesions, characterized by necrobiosis of the hepatic cells and polymorphonuclear infiltration, these cells likewise involved by necrobiosis. The adjacent liver cells frequently displayed some increase of bile pigmentation. These foci were always intralobular

and in 16 instances were perivascular, either adjacent to the central vein or to the sublobular vein.

The *subacute lesions* differed from the acute only in that they were more discrete and the lymphoid cells predominated. Polymorphonuclear cells were relatively scanty. These lesions also were intralobular and four were perivascular.

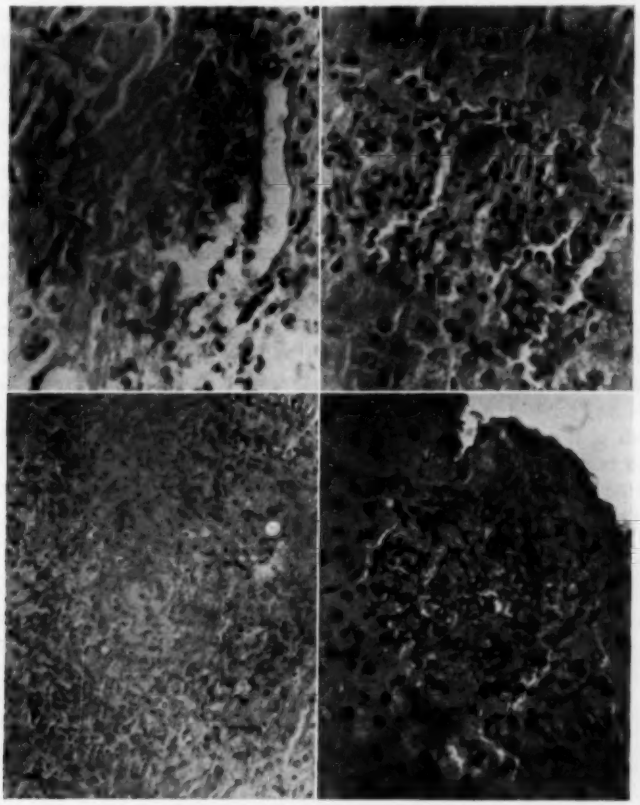


FIG. 5. (Upper left) Periphlebitic focal necrosis near a sublobular vein
FIG. 6. (Upper right) Early tubercle with caseation necrosis and giant cells
FIG. 7. (Lower left) Early caseous tubercle
FIG. 8. (Lower right) Early caseonecrotic tubercle

Tubercle bacilli were not demonstrated in twenty sections chosen as representative of the first four groups.

Fatty metamorphosis in the specimens of hepatic tissue examined varied from moderate to marked in degree. Minor fatty changes were disregarded.

Cirrhosis was diagnosed when the portal area showed fibroblastic response,

usually associated with some degree of cellular inflammation and bile duct proliferation. Because of the small size of the liver fragment, the architectural distortion and nodular pattern were not discernible unless the cirrhosis was extensive. Nodule formation, however, was occasionally seen. Acute focal necroses were sometimes seen at the periphery of the cirrhotic lesion but were interpreted as an indication of the activity of the cirrhosis. This feature of cirrhosis has previously been reported (25).

Periportal inflammation consisted only of the presence of lymphoid cells. The productive features of cirrhosis were absent. The lesions designated in table 1 as *nuclear glycogen deposits* and *increased intracellular bile* had the well-recognized features (a narrow rim of nuclear chromatin and an extraordinarily deep pigmentation of the cytoplasm by bile, respectively) of these lesions.

Tests of Hepatic Function

A total of 634 tests of hepatic function were performed. In 54 instances, the globulin was elevated (3.3–5.9 mg. per 100 cc.); while in 12, the albumin was lowered (3.4-2.8 mg. per 100 cc). The albumin-globulin ratio was inverted in 14 cases. The total proteins were increased in 35 patients (8.1–9.6 mg. per 100 cc.) and decreased in 3 (5.8–4.9 mg. per 100 cc.). The thymol turbidity was abnormally high in 22 patients (5.5–15 u.). The total serum cholesterol value was higher than normal in 7 (264–360 mg. per 100 cc.) and lower in 15 cases (70–154 mg. per 100 cc.). Significant lowering of the cholesterol ester percentage was seen in 2 patients. Bromsulfalein retention greater than 6 per cent in 45 minutes occurred ten times. A decreased amount of prothrombin was seen in 2 patients and increased serum bilirubin in 3. The serum alkaline phosphatase was increased in 10 patients.

Clinical Observations

The extent of the pulmonary tuberculosis, classified according to the National Tuberculosis Association, was minimal in 4 patients, moderately advanced in 26, and far advanced in 40 patients. A comparison of the patient's weight at the time of hepatic biopsy with that prior to the onset of illness was employed as an index of nutrition. Fifty-two patients were below their usual weight, while 18 had maintained their weight. A palpable liver was found in 3 patients, one of whom had ascites.

DISCUSSION

The pathologic lesions in this series vary considerably from those found in series of fatal cases of tuberculosis examined at autopsy. Although in the past little attention has been paid to focal necroses, they were the most frequently observed lesions in the present study. Contrariwise, definite tubercle formation was discovered in only 13 per cent of the biopsied cases as compared to the 63–99 per cent seen in necropsied cases. The 20 per cent incidence of fatty metamorphosis was also considerably lower than the 34–42 per cent reported in autopsy material. Tuberculosis is stated to be one of the commonest causes of

fatty metamorphosis of the liver (26), but the findings in the present series suggest that the fatty change is unrelated to tuberculosis per se. Nine of the 14 patients with fatty metamorphosis gave histories of excessive alcohol consumption and dietary insufficiency. Eleven of the 14 were among 32 patients from whom biopsies were obtained within 18 days of admission; the remaining 3 were among 38 in whom biopsy was performed between the eighteenth and three hundred fifty-sixth hospital days. These facts support the interpretation that alcoholism and undernutrition, rather than tuberculosis, are responsible for the fatty metamorphosis. Eight of the 13 patients with histologic evidence of cirrhosis gave histories of alcoholism. Only 2 patients with cirrhosis denied both alcoholism and loss of weight.

A low concentration of serum cholesterol was more frequent in patients with far advanced pulmonary lesions and was more closely parallel to the clinical course than any other functional test. Two of the patients with low serum cholesterol died of pulmonary tuberculosis subsequent to the completion of this study.

The other tests of hepatic function could not be correlated either with the pathologic findings or the clinical observations. It was interesting to note, however, that in 5 patients with high serum globulin values the hepatic tissue obtained by biopsy revealed no abnormalities on histologic examination. It was also found that there was no difference in the histologic or other laboratory findings in those patients who had received PAS and streptomycin in the past, those who were receiving these drugs during the study, and those who had not received them at all.

SUMMARY

1. Clinical, functional, and histologic investigations of the liver in 70 patients with pulmonary tuberculosis are reported.

2. Nonspecific focal necrosis, always intralobular and frequently periphlebitic, was the most common lesion found.

3. Definite tubercle formation was comparatively infrequent.

4. Fatty metamorphosis was moderately frequent and appeared more closely related to undernutrition than to tuberculosis per se.

5. Cirrhosis was more closely related to alcoholism and undernutrition than to tuberculosis.

6. A low total serum cholesterol was more frequent with far advanced pulmonary lesions and was more closely parallel to the clinical course than was any other functional test.

SUMARIO

Estudio Clínico, Funcional y Biópsico del Hígado en la Tuberculosis Pulmonar

1. Investigaciones clínicas, funcionales e histológicas del hígado fueron llevadas a cabo en 70 enfermos con tuberculosis pulmonar.

2. Necrosis focal anespecífica, siempre intralobular y frecuentemente periflebítica, fué la lesión encontrada más frecuentemente.

3. La formación bien definida de tubérculos fué comparativamente rara.

4. La metamórfosis adiposa fué moderadamente frecuente y pareció estar más enlazada con la desnutrición que con la tuberculosis misma.

5. La cirrosis estaba más íntimamente relacionada con el alcoholismo y la desnutrición que con la tuberculosis.

6. Un bajo nivel de colesterol total fué más frecuente en las lesiones pulmonares muy avanzadas y reflejó la evolución clínica más íntimamente que ninguna otra prueba funcional.

RESUME

Etude clinique et fonctionnelle du foie avec biopsie par ponction dans la tuberculose pulmonaire

1. L'étude clinique, fonctionnelle et histologique du foie a été pratiquée chez 70 malades atteints de tuberculose pulmonaire.

2. La lésion la plus commune qui ait été rencontrée a été un foyer de nécrose sans spécificité, toujours intralobulaire et parfois périveineux.

3. La formation d'un véritable tuberculome était relativement rare.

4. La fréquence de la dégénérescence graisseuse a été peu marquée, elle semble plutôt être en relation avec un état de dénutrition qu'avec la tuberculose elle-même.

5. La cirrhose était plus intimement liée à l'alcoolisme et au défaut de nutrition qu'à la tuberculose.

6. Le taux du cholestérol a été plus fréquemment bas dans les cas de tuberculose avancée et plus étroitement parallèle au cours de l'évolution clinique de l'affection que tout autre test fonctionnel.

REFERENCES

(1) Rolleston, H., and McNee, W.: Diseases of the Liver, Gall Bladder and Bile Ducts, ed. 3, MacMillan and Co., London, 1929.

(2) Warthin, A. S.: The occurrence of icterus in tuberculosis, Internat. Clin., 1911, *1*, 89.

(3) Saphir, O.: Changes in the liver and in the pancreas in chronic pulmonary tuberculosis, Arch. Path., 1929, *7*, 1026.

(4) Ullom, J. T.: The liver in tuberculosis, Am. J. M. Sc., 1909, *137*, 604.

(5) Torrey, R. G.: The occurrence of miliary tuberculosis of the liver in the course of pulmonary tuberculosis, Am. J. M. Sc., 1916, *151*, 549.

(6) Parini, F.: Studio anatomico-istologico del fegato nella enterite tubercular cronica, Sperimentale, Arch. di biol., 1941, *95*, 65.

(7) Jones, J. M., and Peck, W. M.: Incidence of fatty liver in tuberculosis with special reference to tuberculous enteritis, Arch. Int. Med., 1944, *74*, 371.

(8) Janbon, M., Cazal, P., and Bertrand, L.: La ponction biopsie du foie dans les tuberculoses miliares, Presse med., 1949, *57*, 854.

(9) Craddock, C. G., and Meredith, H. C.: Punch liver biopsy in the diagnosis of miliary tuberculosis: Report of a case, New England J. Med., 1949, *241*, 527.

(10) Eichelberger, L., and McCluskey, K. L.: Chemical studies in tuberculosis, Arch. Int. Med., 1927, *40*, 831.

(11) Sweany, H. C., Weathers, A. T., and McCluskey, K. L.: Blood chemistry in tuberculosis, Am. Rev. Tubere., 1924, *8*, 405.

(12) Seibert, F. B., and Nelson, J. W.: Electrophoresis of serum, Am. Rev. Tubere., 1943, *47*, 66.

(13) King, S. E., and Brugger, M.: Plasma cholesterol in tuberculosis and amyloid disease, Ann. Int. Med., 1935, *8*, 1427.
(14) Kruger, A. L., and Gerber, I. E.: Bromsulphalein liver function test in pulmonary tuberculosis, Am. Rev. Tubere., 1942, *46*, 430.
(15) Hurst, A., Maier, H. M., and Lough, S. A.: Studies of hepatic function in pulmonary tuberculosis, Am. J. M. Sc., 1947, *214*, 431.
(16) Savacool, J. W.: Prothrombin studies in pulmonary tuberculosis, Am. J. M. Sc., 1941, *201*, 830.
(17) Steidl, J., and Heise, F. H.: Studies of liver function in advanced pulmonary tuberculosis, Am. J. M. Sc., 1933, *186*, 631.
(18) MacLagen, N. D.: The thymol turbidity test as an indicator of liver dysfunction, Brit. J. Exper. Path., 1944, *25*, 234.
(19) Malloy, H. J., and Evelyn, K. A.: The determination of bilirubin with the photoelectric colorimeter, J. Biol. Chem., 1937, *119*, 481.
(20) Ducci, H., and Watson, C. J.: Quantitative determination of the serum bilirubin with special reference to the prompt reading and the chloroform soluble types, J. Lab. & Clin. Med., 1945, *30*, 293.
(21) Kingsley, C. R., and Schaffert, R. R.: Determination of free and total cholesterol by direct chloroform extraction, J. Biol. Chem., 1949, *180*, 315.
(22) Gornall, A. G., Bardawill, C. J., and David, M. M.: Determination of serum proteins by means of the biuret reaction, J. Biol. Chem., 1949, *177*, 751.
(23) Bodansky, A.: Phosphatase studies: Determination of serum phosphatase, factors influencing the accuracy of the determination, J. Biol. Chem., 1933, *101*, 93.
(24) Aggeler, P. M., Howard, J., Lucia, S. P., Clark, W., and Astaff, A.: Standardization of the Quick prothrombin test, Blood, 1946, *1*, 220.
(25) Hart, J. F., and Lisa, J. R.: Histogenesis of Laennec's cirrhosis, New York State J. Med., 1937, *37*, 1619.
(26) Lichtman, S. S.: Diseases of the Liver, Gall Bladder, and Bile Ducts, ed. 2, Lea and Febiger, Philadelphia, 1949.

RIBS FROM THORACOPLASTY AS A POSSIBLE SOURCE OF HOMOGENOUS BONE GRAFTS[1]

PAUL F. HAUSMANN

(Received for publication June 15, 1950)

INTRODUCTION

Since the practicability of homogenous bone grafts has been demonstrated, such grafts have been successfully employed by orthopedic surgeons for various fusion procedures on tuberculous lesions of bone (1, 2, 3). In 5 patients operated upon at Muirdale Sanatorium, the source of these grafts has been the rib fragments removed from other tuberculous patients during the course of thoracoplasty for pulmonary disease. The usual precautions advocated in the choice of bone donors in respect to history of jaundice and the presence of syphilis or other infectious or neoplastic disease were taken. It was believed that the use of bone from thoracoplasty patients in these 5 instances was not to be regarded as objectionable, as the bone lesions of the recipient were of tuberculous etiology. The use of homogenous bone grafts was introduced on this service by the orthopedic surgeons in order to shorten the grafting operation. When autogenous bone grafts are used, a second surgical procedure, taking the graft, is added to an already protracted and laborious operation, thereby greatly lengthening the time consumed in the total procedure.

Reasonable selection of bone donors was automatically exercised since thoracoplasty is not employed in the treatment of patients with evidence of disseminated tuberculosis. Further selection was practiced in that no rib was employed which was resected from patients with obvious or questionable chest wall disease.

Preservation of rib fragments: In those instances in which thoracoplasty rib fragments were employed as grafts, they were placed in sealed sterile glass containers immediately following resection and stored for a period of several days to two weeks in an ordinary household deep-freeze unit in which the temperature was maintained at $-10°$ to $-20°$F. It has been established that the viability or virulence of *M. tuberculosis* is unaffected by cold, even that of liquid air itself (4). Therefore, the refrigeration process, which is the usual method of preserving bone for bone banks, could not be expected to affect the viability of the tubercle bacilli which might be present in the rib fragments.

Since it was not possible to find any satisfactory information in the literature regarding the possibility of transmission of tuberculosis by such use of resected ribs from thoracoplasties, it was believed that a bacteriologic study should be made in order to obtain evidence which might be useful in evaluating the hazard or safety of their use as bone grafts. It is to be emphasized that the present study is not concerned with the advisability from the surgical standpoint of using

[1] From the Surgical Services, Muirdale Sanatorium, Wauwatosa, Wisconsin, and the Marquette University School of Medicine.

thoracoplasty ribs as grafts but merely whether their use might be a source of tuberculous infection. Moreover, it is realized that in order to establish the absolute statistical probability of infection by this route, studies on many more resected rib fragments would be necessary than are herein reported. Nevertheless it is believed that the present preliminary report is warranted in order to focus attention on the problem and hence lead to the accumulation of sufficient data to answer the question.

OBSERVATIONS

Segments of ribs from sixty-nine consecutive thoracoplasty stages on 34 patients were studied. Since thoracoplasty stages at this sanatorium are spaced at an interval of three weeks, specimens from several separate surgical procedures on the same patient were included.

Under aseptic technique, the resected rib was compressed by means of a rib-holding forceps immediately upon removal, and the expressed marrow was collected in a sterile test tube containing a few drops of sterile saline solution. A direct marrow smear was made at this time. The marrow saline mixture was then digested by means of potassium hydroxide, neutralized, and cultured for a period of eight weeks on Petragnani medium in the manner usually employed for culture of tubercle bacilli in pulmonary secretions. Scrapings from the surface of the rib were similarly cultured. In no instance were acid-fast bacilli found in the direct marrow smears, and there was no growth of tubercle bacilli in either bone surface cultures or in the marrow digest cultures.

COMMENT

It is probable that no implantation of tubercle bacilli into the recipient's tissues would have taken place if any of the fragments studied in this series had been employed as homogenous bone grafts. Moreover, in the five instances in which the rib fragments were actually used there was no induration or other evidence of infection in any of the wounds, and the bone grafts and fusions have been judged satisfactory and successful by the orthopedic surgeons. The series is too small, however, to permit the categorical statement that the likelihood of implantation of tubercle bacilli into recipient's tissues is small if such material were routinely employed as a source of bone grafts. It is to be hoped, therefore, that similar cultural studies will be obtained in a number of surgical clinics so that the question of the risk of infection by this procedure can be definitely answered.

SUMMARY

1. Segments of ribs from sixty-nine consecutive thoracoplasty stages on 34 patients were examined for tubercle bacilli by means of direct smear, marrow digest cultures, and surface-scraping cultures in an attempt to demonstrate the likelihood of implantation of organisms into the recipient if such fragments were employed as bone grafts.

2. In no instance were tubercle bacilli found in the material studied.

3. In 5 instances, rib fragments from thoracoplasty patients were successfully employed as homogenous bone grafts for tuberculous lesions of bone.

SUMARIO

Las Costillas Procedentes de las Toracoplastias como Posible Fuente de Injertos Oseos Homógenos

1. Segmentos de costillas extirpadas en 69 tiempos consecutivos de toracoplastias en 34 enfermos consecutivos fueron examinados en busca de bacilos tuberculosos por medio de frotes directos, cultivos de digestos de médula ósea y cultivos de raspados superficiales, tratando de determinar la probabilidad de implantar microbios en el enfermo si se empleaban dichos fragmentos para injertos óseos.

2. En ningún caso de descubrieron bacilos ácidorresistentes en el material estudiado.

3. En 5 casos, empleáronse con éxito fragmentos costales de enfermos tratados con toracoplastias como injertos óseos homógenos por lesiones tuberculosas de los huesos.

RESUME

Les côtes provenant de thoracoplasties comme source de greffes osseuses homogènes

1. Des fragments de côtes prélevées à la suite de 69 thoracoplasties consécutives, pratiquées à différents stades sur une série de 34 malades, ont été examinés pour y rechercher le bacille tuberculeux par examen direct de frottis, et des cultures d'extraits de moelle osseuse et d'éléments prélevés par grattage superficiel ont été faites pour essayer de démontrer la possibilité d'inoculer l'organisme quand des tissus de cette provenance sont utilisés chez le receveur comme greffons osseux.

2. En aucun cas la présence de bacilles acido-résistants n'a éte décelée dans les tissus étudiés.

3. Dans 5 cas, des fragments de côtes prélevés sur des malades, au cours de la thoracoplastie, ont été employés avec succès comme greffons osseux dans des cas de tuberculose osseuse.

REFERENCES

(1) Bush, L. F.: The use of homogenous bone grafts, J. Bone & Joint Surg., 1947, *29*, 620.
(2) Wilson, P. D.: Experiences with a bone bank, Ann. Surg., 1947, *126*, 932.
(3) Inclan, A.: The use of preserved bone graft in orthopaedic surgery, J. Bone & Joint Surg., 1942, *24*, 81.
(4) Galtier, Cadeac, Malet, Moussu: Compt. rend de. la. Caisse nat. d. recherches sci., 1912. Quoted by Calmette, A. in *Tubercle Bacillus Infection and Tuberculosis in Man and Animals*, Baltimore, Williams & Wilkins Company, 1923, p. 50.

THE ABSORPTION OF THE SODIUM SALT OF PARA-AMINOSALICYLIC ACID (PAS) FROM THE RECTUM[1]

CHARLES W. RIEBER, HERTA KUSCHINSKI, AND MAX M. FRIEDMAN

(Received for publication July 19, 1950)

In the past six years, since Lehmann (1) and his co-workers introduced para-aminosalicylic acid (PAS) for the treatment of tuberculosis, considerable experimental and clinical work has been done with this compound. Investigations were carried out in Sweden by Lehmann (2), Vallentin (3), and others, and in England by Dempsey and Logg (4), Nagley (5), and Erdei (6). *In vitro* and *in vivo* studies were made in this country by Youmans (7, 8, 9) and by Feldman (10) and their respective associates, and it was found that low concentrations of PAS, usually less than 1 γ per ml. of medium inhibited virulent strains of *M. tuberculosis*.

It was soon observed that, although large doses of PAS could be given orally without causing generalised toxic reactions, frequent difficulty was encountered because of gastrointestinal symptoms which were so severe in some patients as to necessitate the cessation of treatment (11–15). Many variations in the method of administration of the drug have been undertaken to overcome this complication. Nagley and Logg (5) reported that the sodium salt of PAS gave fewer side effects but that, when larger doses were used, two-thirds of their patients complained of gastrointestinal disturbances. The present writers have had a similar experience with the use of sodium PAS when administered by the oral route.

The sodium salt of PAS in isotonic solution has a pH of 7.3 and can be given intravenously and intrapleurally as well as orally. It is interesting to note that, when sodium PAS has been administered intravenously, nausea does not develop until rather high concentrations have been attained in the blood (16). An excellent review of this subject has recently been published by Bogen (17).

As sodium PAS is readily soluble and easily absorbed, it seemed to the present writers that it might be possible to attain therapeutically effective concentrations of the drug in the blood by rectal administration. Accordingly, the present study was undertaken to determine whether sodium PAS could be administered by rectum without undue irritation and whether the therapeutically effective concentrations of the drug could be attained in the blood by use of this route of administration.

Methods

A 20 per cent solution of sodium para-aminosalicylate, "Parasal Sodium,"[2] was used in this study. This solution is supplied in 100-milliliter ampules for intravenous use, and has a

---

[1] From the Medical Service of the Triboro Hospital and the Department of Laboratories of Queens General Hospital, Jamaica 2, N. Y.

[2] "Parasal Sodium" is the proprietary name of a 20 per cent solution of sodium para-aminosalicylate obtained from the Panray Corporation of New York City. The authors are indebted to the Panray Corporation for supplying the drug for this study.

pH of 7.3. By using the prepared solution the uniformity of the material was assured throughout the period of our investigation. The subjects studied were all female patients on the tuberculosis service, most of whom had been unable to continue treatment with PAS because of gastrointestinal symptoms. At the time of the study the patients were receiving no other medication. Four series of experiments were conducted, with results which may be seen in tables 1 to 4. In all cases one week was allowed to elapse between the oral and the rectal administration of the drug. The rectal dose was administered by the insertion of a rectal tube after the subject had emptied her bladder and after a small low saline enema had been given to cleanse the lower bowel. The foot of the bed was then raised approximately twelve inches and the subject remained quietly in this position for one to three hours. Most rectal instillations were given in a volume of 60 ml., since it was found that any larger volume gave rise to cramps and a desire to evacuate the bowel. Aside from the formation of a small amount of mucus during the time that the drug was in the rectum, no other symptoms were noted.

The method for determining the plasma concentrations of free PAS was essentially that of Bratton-Marshall as modified by Way and associates (19).

RESULTS

In table 1 may be seen a comparison of the plasma concentrations attained in 4 subjects after administration of 6 gm. of sodium PAS by the oral and by the rectal routes. It is noted that peak concentrations are found after oral administration at two hours and that there is a rather sharp drop at four hours. This agrees with the findings of Dye (18), Erdei (6), and Way and his associates (19). The peak plasma concentrations attained after rectal administration of 6 gm. are between one-half and one-fourth of the concentration attained after oral administration, but do not show as sharp a drop at four and at six hours after the drug is given. If 1 mg. per 100 ml. of PAS is arbitrarily designated as the "bacteriostatic" concentration and between 3 and 7 mg. per 100 ml. of plasma as the "therapeutic" concentration (17, 18), it may be seen that bacteriostatic concentrations are present up to six hours after administration by both the rectal and the oral routes, and therapeutic concentrations persist up to four hours. Thus, it would be necessary to repeat the rectal dose every four hours in order to maintain a good therapeutic concentration for the twenty-four-hour period. It has not been definitely determined, however, that effective concentrations of PAS need be maintained continuously for maximum therapeutic effects.

In the next experiment, two doses of sodium PAS of 6 gm. each were given at twelve-hour intervals and the plasma concentrations were determined up to twenty-four hours to see whether there would be a cumulative effect from the second dose. It was also desired to discover whether patients could tolerate two doses per day by rectum. In table 2 the results are shown in a series of 6 subjects. The findings are similar to those of the previous experiment (table 1) in that the peak plasma concentrations attained after rectal administration of 6 gm. of sodium PAS are between one-half and one-fourth the concentrations attained following oral administration of the same dose. It also may be seen (table 2) that the twelve-hour- and twenty-four-hour—plasma concentrations were the same in all cases, so that there is no cumulative effect from a second dose of sodium PAS given after a twelve-hour interval. The plasma concentrations attained eight hours after rectal administration are approximately the same as

when the same dose is given by the oral method and are below the therapeutic range.

TABLE 1

PAS Plasma Concentrations Mg. Per 100 Ml. after a Single Six-gram Dose

PATIENT	METHOD	HOURS AFTER DOSE				
		1	2	4	6	8
V. P.	Oral	17.4	19.0	8.9	2.9	1.2
	Rectal	5.4	6.8	5.7	4.6	
E. S.	Oral	16.5		6.5	3.1	0.9
	Rectal	4.0	4.2	3.4	1.9	
E. Z.	Oral	11.8	13.9	4.9	1.1	0.6
	Rectal	5.8	6.5	4.0	1.7	
A. G.	Oral	9.2	12.1	4.1	0.7	0.7
	Rectal	4.0	4.1	2.0	1.1	

TABLE 2

PAS Plasma Concentrations Mg. Per 100 Ml. after Two Six-gram Doses Twelve Hours Apart

PATIENT	METHOD	HOURS AFTER FIRST DOSE					
		2	4	6	8	12	24
V. P.	Oral	23.1	11.5	4.7		0.6	0.9
	Rectal	7.5	5.5	1.4	1.2		1.3
J. R.	Oral	19.6	11.5	5.5		0.4	0.5
	Rectal	7.5	4.8	1.9	0.6		0.0
E. H.	Oral	13.0	7.2	2.4		0.2	0.3
	Rectal	4.5	3.6	2.4	1.1	0.4	0.1
G. S.	Oral	7.4	5.2	1.5		0.3	0.4
	Rectal	4.5	2.5	1.4	0.8	0.4	0.6
J. G.	Oral	12.7	4.2	1.3		0.3	
	Rectal	4.6	2.1	0.9	0.7	0.3	0.5
E. F.	Oral	13.2	7.6	2.8		0.3	0.0
	Rectal	5.1	2.9	1.6	0.8	0.5	0.1

In a third group of 6 subjects, 12 gm. of sodium PAS were given by rectum to determine whether higher concentrations could thus be attained in the blood and whether any adverse symptoms would occur from this dose. It was not thought advisable to administer so large an amount of drug in a single dose by mouth. It may be seen from table 3 that the plasma concentrations attained in

most subjects two hours after rectal administration of 12 gm. of sodium PAS approximated the values attained when 6 gm. of drug were given by the oral route. The plasma concentrations following this large dose by rectum declined rapidly within four hours. In 4 subjects this decline could be accounted for by the fact that they were given the 12 gm. of sodium PAS in 120 ml. of solution and developed cramps and the desire to evacuate the bowel. Thus, the longest period the solution was retained was three hours, whereas the usual length of time the 6-gram rectal dose could be retained was four to six hours. Two subjects were given only 60 ml. of solution containing 12 gm. of sodium PAS and were able to keep the drug in the rectum for seven to nine hours. The reason

TABLE 3

PAS Plasma Concentrations Mg. Per 100 Ml. after a Single Twelve-gram Rectal Dose

PATIENT	HOURS AFTER DOSE					
	2	4	6	8	12	24
G. S.	22.5	4.3	1.4	0.4	0.2	0.1
E. H.	8.8	4.6	2.8	2.4	0.6	0.1
J. R.	13.0	9.0	2.8	1.5	0.5	0.1
V. P.	10.1	7.6	2.8	1.2		0.4
E. F.	20.5	15.6	6.9	2.7	0.8	0.2
J. G.	8.9	4.1	1.7	0.8	0.2	

TABLE 4

PAS Plasma Concentrations Mg. Per 100 Ml. after Three Eight-gram Doses of PAS by Rectum Four Hours Apart

PATIENT	HOURS AFTER FIRST DOSE					
	2	4	6	8	12	24
D. M.	6.4	3.7	8.9	4.3	3.5	0.3
N. Z.	5.1	2.7	7.1			

for the low plasma concentrations of drug in patient J. G. is unexplained but such variation in plasma concentrations in certain patients has been noted by other investigators (18, 19, 20). Those subjects who received a total volume of only 60 ml. by rectum, whether it contained a dose of 6 or 12 gm., had no complaints except that the sodium PAS apparently acted as a mild diuretic, and frequent urination made it difficult for them to retain the solution of drug in the rectum.

An attempt to give 8 gm. every four hours by rectum demonstrated that more time must elapse between rectal instillations. When the tube was inserted for the second and third doses, some of the previous solution was partially evacuated through the tube. In the first subject in table 4, it may be seen that a rise of the plasma concentration was present at six hours and that there was still a

therapeutic concentration present at twelve hours after administration of the drug. A similar second rise in the plasma concentration six hours after the first rectal instillation occurred in the other subject in this experiment (table 4).

COMMENT

The value of PAS in the therapy of tuberculosis has been established by many studies during the past six years. One of the drawbacks in the use of this drug in therapy has been the nausea and vomiting and other gastrointestinal symptoms associated with adequate dosage. It was hoped in this investigation that by the rectal route of administration adequate plasma concentrations of drug could be produced in those people who were subject to gastrointestinal symptoms when the drug was given by mouth. It was found that plasma concentrations within the therapeutic range were attained for two to four hours after a dose of 6 gm., and excellent plasma concentrations in most cases up to six hours after a dose of 12 gm. of sodium PAS by rectum. These plasma concentrations can be achieved without the production of any gastrointestinal symptoms in patients who had had these symptoms from oral administration of PAS. The four-hour repeated rectal administration of sodium PAS is impracticable because the previously instilled solution tends to be evacuated through the tube. However, a schedule of two doses administered twelve hours apart might be practicable by the rectal route if the plasma concentrations could be maintained throughout the twelve-hour period. A recent report by Boger and Pitts (21) indicates that the use of *p*-(di-n-propylsulfamyl)-benzoic acid "Benemid" retards the conjugation and excretion of PAS. They found that, by giving 0.5 gm. of "Benemid" every six hours for twenty-four hours before the sodium PAS was administered, they could extend adequate plasma concentrations up to four hours after a single 4-gram dose. They also found that with "Benemid" the plasma concentrations of PAS were elevated 2.3 to 4.1 times. It might be possible to obtain adequate concentrations with two doses of 12 gm. of sodium PAS twelve hours apart given rectally, when 0.5 gm. of "Benemid" is given every six hours during treatment.

SUMMARY

A comparison has been made between the plasma concentrations of PAS obtained following administration of equivalent doses of sodium PAS orally and by rectum. It was found that, when the same doses were given orally or rectally to the same subjects, plasma concentrations attained in the first two hours after ingestion were two to three times those attained after rectal administration of the drug. Beginning with the sixth hour after administration, comparable concentrations were attained following both methods. Therapeutic concentrations were maintained up to four hours after the drug was administered by rectum. A dose of 12 gm. by rectum gave plasma concentrations similar to those following the administration of 6 gm. by mouth, and there appeared to be slower absorption and better maintenance of adequate plasma concentrations when the subject was able to retain the solution for more than four hours.

SUMARIO

La Absorción por el Recto de la Sal Sódica del Acido Para-Amino-salicílico (PAS)

En este estudio, hízose una comparación entre las concentraciones de PAS obtenidas en el plasma después de la administración de dosis equivalentes de dicha droga por vía oral y por el recto. Comparando dosis idénticas administradas oral y rectalmente en los mismos enfermos, los tenores plasmáticos obtenidos en las primeras dos horas por vía oral fueron dobles o triples que los obtenidos por vía rectal. A partir de la sexta hora, las cifras tendieron a ser iguales con ambas técnicas. Con la técnica rectal se mantuvieron niveles terapéuticos hasta cuatro horas. Una dosis de 12 gm. por el recto dió cifras plasmáticas semejantes a las conseguidas con 6 gm. por vía bucal, y al parecer la absorción era más lenta y se mantenían mejor niveles adecuados en el plasma cuando el sujeto podía retener la solución más de cuatro horas.

RESUME

Absorption du sel de sodium de l'acide para-amino-salicylique (PAS) au niveau du rectum

Les concentrations de PAS dans le sang après l'administration d'une dose équivalente de ce composé par voie orale et par voie rectale ont été comparées.

La comparaison de la concentration sanguine a été faite dans les deux heures suivant l'administration de doses semblables, chez un même malade, tantôt par voie orale et tantôt par voie rectale; on a constaté que la concentration consécutive à l'administration orale était deux fois à trois fois plus élevée.

A partir de la sixième heure les taux de concentrations tendent à devenir égaux, après l'un ou l'autre de ces deux modes d'administration. Des concentrations thérapeutiques ont été maintenues jusqu'à quatre heures après l'administration rectale. Avec une dose de 12 g. par voie rectale la concentration a été la même que celle obtenue avec 6 g., par voie orale, l'absorption a semblé plus lente et la concentration dans le sérum s'est maintenue à un taux adéquat quand le malade a été capable de retenir la solution pendant plus de quatre heures.

REFERENCES

(1) Lehmann, J.: Para-aminosalicylic acid in the treatment of tuberculosis: Preliminary communication, Lancet, 1946, *1*, 15.

(2) Lehmann, J.: Chemotherapy of tuberculosis: Bacteriostatic effect of *p*-aminosalicylic acid and related derivatives on tubercle bacilli: Experimental and clinical studies, Svenska läk.-tidning, 1946, *43*, 2029. (Pharmaceut. Abst. 13, 191, in J. Am. Pharm. A. (Sc. Ed.) 36, June 1947.)

(3) Vallentin, G.: Clinical observations on the treatment of pulmonary tuberculosis by *p*-aminosalicylic acid, Svenska läk.-tidning, 1946, *43*, 2047.

(4) Dempsey, P. G., and Logg, M. H.: Para-aminosalicylic acid in tuberculosis: Early results of clinical trails, Lancet, 1947, *2*, 871.

(5) Nagley, M. H., and Logg, M. H.: *p*-Aminosalicylic acid in pulmonary tuberculosis, Lancet, 1949, *2*, 913.

(6) Erdei, A.: *p*-Aminosalicylic acid in tuberculosis, Lancet, 1948, *2*, 118.

(7) Youmans, G. P.: The effect of *p*-aminosalicylic acid *in vitro* and *in vivo* on virulent human tubercle bacilli, Quart. Bull., Northwestern Univ. M. School, 1946, *20*, 420.

(8) Youmans, G. P., Youmans, A. S., and Osborne, R. R.: The combined effect of streptomycin and p-aminosalicylic acid on experimental tuberculosis in mice, Journal-Lancet, 1947, *67*, 403.

(9) Youmans, G. P., Raleigh, G. W., and Youmans, A. S.: The tuberculostatic action of p-aminosalicylic acid, J. Bact., 1947, *54*, 409.

(10) Feldman, W. H., Karlson, A. G., and Hinshaw, H. C.: p-Aminosalicylic acid in experimental tuberculosis in guinea pigs, Proc. Staff Meet., Mayo Clin., 1947, *22*, 473.

(11) Lehmann, J.: The treatment of tuberculosis in Sweden with para-aminosalicylic acid: A review, Dis. of Chest, 1949, *16*, 684.

(12) Saucheray, P. H., and Tucker, W. B.: Notes on toxicity of p-aminosalicylic acid, Tr. Eighth Streptomycin Conference of the Veterans Administration, November 10, 1949.

(13) Shamaskin, A.: Rate of absorption and toxicity of p-aminosalicylic acid: Comparative study of enteric-coated capsules, powder, and solution of sodium p-aminosalicylic acid, Tr. Eighth Streptomycin Conference of the Veterans Administration, November 10, 1949.

(14) Dunner, E., Brown, W. B., and Wallace, J.: The effect of streptomycin with para-aminosalicylic acid on the emergence of resistant strains of tubercle bacilli, Dis. of Chest, 1949, *16*, 661.

(15) Eastlake, C., Jr., and Barach, A. L.: Use of PAS in chronic pulmonary tuberculosis, Dis. of Chest, 1949, *16*, 1.

(16) Barclay, W. R.: Intravenous administration of PAS, Am. Rev. Tuberc. 1949, *60*, 385.

(17) Bogen, E., Loomis, R. N., and Will, D. W.: PAS treatment of tuberculosis: A review, Am. Rev. Tuberc., 1950, *61*, 226.

(18) Dye, W. E.: The concentration of para-aminosalicylic acid in the blood during various regimens, Tr. Seventh Streptomycin Conference of the Veterans Administration, April 1949.

(19) Way, E. L., Smith, P. K., Howie, D. L., Weiss, R., and Swanson, R.: The absorption, distribution, excretion, and fate of p-aminosalicylic acid, J. Pharmacol. & Exper. Therap., 1948, *93*, 368.

(20) Vennesland, K., Ebert, R. H., and Bloch, R. G.: *In vitro* effect of streptomycin and p-aminosalicylic acid on the growth of tubercle bacilli, Proc. Soc. Exper. Biol. & Med., 1948, *68*, 250.

(21) Boger, W. P., and Pitts, F. W.: Influence of p(di-n-propylsulfamyl)-benzoic acid, "Benemid", on para-aminosalicylic acid (PAS) plasma concentrations, Am. Rev. Tuberc., 1950, *61*, 862.

Case Reports

ESOPHAGOBRONCHIAL FISTULA ASSOCIATED WITH SEVERE HEMORRHAGES[1]

Treated by Surgical Excision and Lobectomy

HERBERT C. MAIER

(Received for publication October 6, 1950)

When an esophagobronchial fistula is large, a history of severe coughing on the ingestion of fluid and food suggests the correct diagnosis and the communication between the air and food passages usually can be proved by routine roentgenograms of the esophagus made during the ingestion of radiopaque material. When the fistulous tract is small, valvelike, or has such a direction that little spillage of esophageal contents into the bronchus occurs, the correct diagnosis may be difficult to establish. Severe hemopytses are not infrequently an outstanding symptom. Some pulmonary suppuration is often present but may not be recognized readily because of minimal purulent expectoration and lack of definite roentgenographic evidence of an intrapulmonary lesion. Two cases of acquired nontraumatic esophagobronchial fistula illustrating these points are reported in this paper.

The occurrence of congenital esophagobronchial fistula is very rare if those cases associated with esophageal atresia are excluded from consideration. Most acquired fistulous communications between the air and food passages are due to cancer. Nonmalignant acquired esophagobronchial fistulas are caused by trauma, tuberculosis, syphilis, infections, and diverticulum of the esophagus; involvement of mediastinal lymph nodes plays a role in some of these conditions.

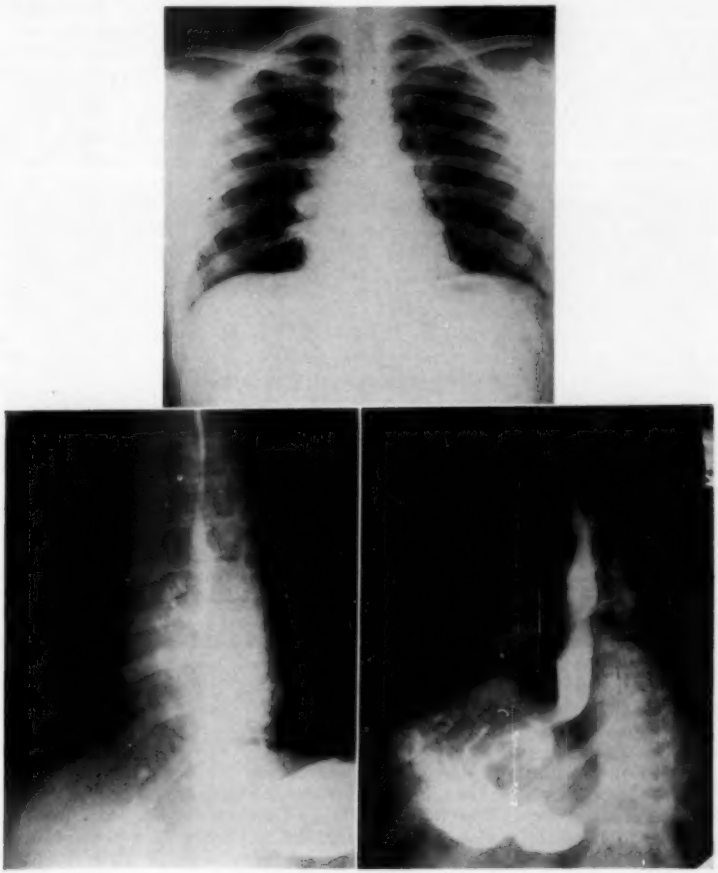
The case mortality from esophagobronchial fistula is high unless a correct diagnosis is made and proper therapy instituted. Surgical treatment is indicated, with few exceptions, unless the fistulous communication is caused by an inoperable cancer. Antimicrobial drugs have aided greatly in the surgical correction of fistulas associated with tuberculosis and other infections.

CASE REPORTS

Case 1. S. W., a 36-year-old male, was in good health without pulmonary or esophageal symptoms until June 1946 when he developed an upper respiratory infection which responded to penicillin. A cough productive of a very small amount of sputum developed at that time. A few months later he expectorated a mouthful of blood. In April 1947, a severe hemoptysis occurred and rales were heard at the base of the right lung posteriorly. Chest roentgenograms showed calcified mediastinal lymph nodes (figure 1). Bronchiectasis was suspected but bronchograms and bronchoscopy were considered negative. The sputum was negative for tubercle bacilli on guinea pig inoculation. Penicillin and streptomycin were administered. Later the various roentgenographic studies were repeated at another hospital, with similar findings; however, a traction diverticulum in the midportion of the esophagus

[1] From the Surgical Service, Lenox Hill Hospital, New York, N. Y.

was revealed on roentgenographic examination of the gastrointestinal tract. A lateral film showed fairly close apposition between this diverticulum and a large calcified lymph node in



Case 1

FIG. 1. (Top) Posteroanterior roentgenogram shows slight increase in density with areas of calcification in the right hilar region.

FIG. 2. (Lower left) Barium in esophagus has outlined a small traction diverticulum which extends to calcified mediastinal lymph nodes. Although a very short small sinus extends from the apex of the diverticulum, no barium has entered the bronchial tree.

FIG. 3. (Lower right) Postoperative roentgenogram shows normal appearing esophagus.

the hilar region, as well as a small tract leading from the diverticulum toward this lymph node (figure 2). Repeated roentgenographic studies with barium and lipiodol failed to demonstrate a fistulous communication between esophagus and bronchus. Hemoptyses became

more frequent and often continued for several days. Clubbing of the fingers then appeared. In January 1948 methylene blue injected into the esophagus through a Levin tube was coughed up. Tube feeding was then instituted and a marked reduction in cough and sputum, with great clinical improvement, ensued. The patient learned to pass the tube himself for each meal. Later he took solid food by mouth and liquids by tube. Guinea pigs were inoculated with two different specimens of sputum containing acid-fast bacilli but they showed no tuberculosis when sacrificed. Penicillin was given over long periods of time and the temperature remained normal. Endoscopic examination by Dr. Paul Holinger revealed a small fistulous opening in the right lateral wall of the esophagus 32 cm. from the upper incisor teeth. The other end of the fistula opened into the posteromedial wall of the right bronchus between the level of the upper and middle lobe orifice. Fused sodium hydroxide was applied to the esophageal end of the fistula without benefit. The patient was then referred by Dr. Saader Goodman for surgical treatment.

Operation: A right transpleural thoracotomy on June 22, 1948 revealed induration of the paramediastinal portion of the right lung in the posterior hilar region. The mediastinal lymph nodes were enlarged and partly calcified. The esophagus was adherent to a mass of calcified nodes. Dissection revealed a fistulous tract approximately 2 cm. in length between the esophagus and the right bronchus. The bronchial end of the fistula contained granulation tissue, whereas at the esophageal end the esophageal mucosa was pulled out by traction. A bronchial vessel in close proximity to the fistula was erroneously assumed to be the probable source of hemoptysis. The fistulous tract was excised together with an adjacent calcified lymph node. The bronchial and esophageal openings were closed with fine silk. A flap of mediastinal pleura was interposed between the bronchial and esophageal sites of closure. No pulmonary tissue was resected because it was incorrectly thought that the relatively small area of induration in the superior segment of the lower lobe was of minor significance. Microscopic examination of the sinus tract showed that most of it was lined by stratified squamous epithelium. The adjacent connective tissue showed a marked chronic inflammatory reaction.

The postoperative course in the hospital was uneventful. Shortly after discharge, however, cough and expectoration reappeared and later hemoptyses recurred. Rales were again heard at the base of the right lung posteriorly. Roentgenographic examination of the esophagus now showed no abnormality (figure 3). The only change in the chest film was a slight increase in the area of density around one of the calcific shadows in the right hilar region. Since no mediastinal abscess had been found in association with the fistulous tract at the original operation, it seemed likely that a pulmonary suppurative focus which was the cause of the bleeding had been overlooked at the first operation.

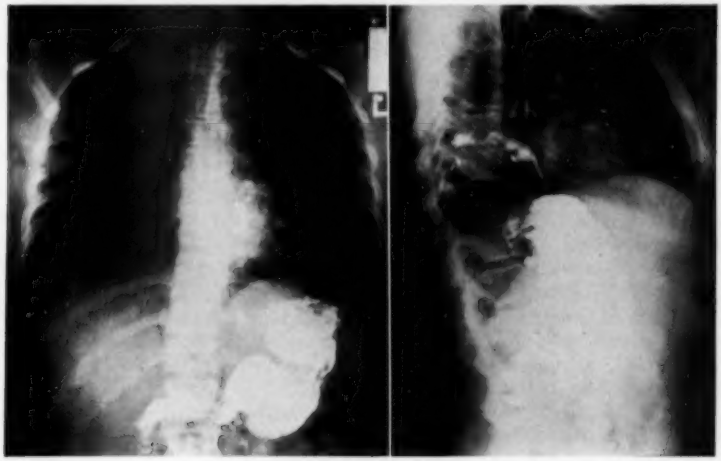
The second operation was performed on August 16, 1948. Since the evidence strongly indicated that the bleeding came from the indurated portion of the right lower lobe, the entire right lower lobe was removed. A segmental resection was not feasible because of the induration at the hilum. When the surgical specimen was examined, it was found that the source of bleeding was a small cavity within the apex of the lower lobe which contained a broncholith. Because of its paramediastinal position this calcification, which had been one of several seen on the roentgenogram, had been assumed to be one of the calcified lymph nodes. Examination of the resected lobe of the lung also revealed chronic pneumonitis and bronchiectasis in the superior segment of the lobe. The lymph nodes showed chronic inflammation and calcification.

The postoperative course was uneventful. No further bleeding has occurred and the patient has been well during the twenty-two months since the lobectomy.

Case 2. V. T., a 31-year-old female, had a history of repeated large hemorrhages for seven years. It was somewhat uncertain whether the blood was coughed up or regurgitated. The bleeding usually occurred at the time of menstruation. On several hospital admissions elsewhere, no definite diagnosis had been established. With careful questioning the patient ad-

mitted that since childhood she had tended to cough on ingesting fluids, but solid food usually caused no trouble. A feeling of difficulty in breathing sometimes occurred when she drank water. She gave no history of purulent expectoration, fever, or other signs of pulmonary suppuration. Roentgenograms of the lungs had been considered to show no definite lesion.

An esophagobronchial fistula was suspected and therefore a roentgenographic examination of the esophagus was performed in various positions. In the upright position a small amount of barium delineated a small outpouching from the lower esophagus (figure 4). With the patient recumbent, more barium ran through the fistula and demonstrated cavities in the lower lobe of the left lung (figure 5). Routine postero-anterior films had not shown the pulmonary lesion because it was hidden by the cardiac shadow.



Case 2

FIG. 4. (Left) Film shows collection of barium outside esophageal lumen.

FIG. 5. (Right) Lateral roentgenogram taken after patient had been supine reveals additional barium extending from fistulous opening into intrapulmonary cavities.

Operation: Operation was performed on October 27, 1948. A left posterolateral incision was employed. Vascular adhesions were present over the lower lobe. Enlarged, vascular lymph nodes were found at the hilum, and the hilar portion of the lobe was indurated. The esophagus was adherent to the lower lobe over a 2-centimeter area just below the inferior pulmonary vein. There was a communication between the esophagus and a cavity in the lung which contained thick, gray, foul material. The opening in the esophagus was closed with two layers of sutures. The left lower lobe was excised. The operative findings suggested that the fistula was not congenital. Examination of the resected portion of the lung revealed a large, irregularly shaped intrapulmonary cavity lined by granulation tissue. Bronchiectasis was present. The esophagobronchial fistula was partly lined by stratified squamous epithelium, but mostly by granulation tissue with a diffuse infiltration of inflammatory cells.

The postoperative course was uneventful. The patient has been well since operation. Barium studies show no esophageal deformity.

DISCUSSION

Coleman and Bunch (1) have reviewed the literature of acquired nonmalignant esophagotracheobronchial fistula for the period 1916 to 1949. In the 75 cases they studied, the etiology was listed as follows: traumatic, 21 cases; tuberculosis, 14 cases; diverticulum of esophagus, 11 cases; syphilis, 11 cases; empyema, 1 case; actinomycosis, 1 case; undetermined, 16 cases. It should be noted that these 75 cases include tracheo-esophageal as well as broncho-esophageal fistulas. In most cases of esophagotracheobronchial fistula due to trauma, a careful history will suggest injury of the esophagus by foreign body or instrumentation, or that there has been a crushing wound of the thorax. Among the cases classified as undetermined in etiology are undoubtedly some fistulas between the food and air passages secondary to an inflammatory process of the mediastinal lymph nodes. The same etiologic factor may operate in cases of fistula associated with diverticulum of the esophagus. These traction diverticula are usually attributed to a periesophageal infection from mediastinal lymphadenitis. In one of the cases here reported, traction on the esophagus had been produced by an adherent calcified lymph node. The later development of a fistulous opening into the esophagus and bronchus may have resulted from the development of a small abscess around the lymph node with secondary rupture into both the esophageal and bronchial lumina.

A traction diverticulum is a common finding in the midthoracic esophagus and very few cause any symptoms unless retention of food within the sac occurs. The writer has seen several patients, however, who apparently did have symptoms caused by this lesion in the absence of roentgenographic evidence of retention within the diverticulum. The patients complained of occasional attacks of malaise, fever, some chest discomfort (perhaps aggravated by swallowing), and in one instance there was swelling of the neck at the time of the febrile episodes. The differential diagnosis seemed to rest between mediastinal lymphadenitis, perhaps associated with a chronic nonspecific mediastinitis, and an inflammatory process associated with the traction diverticulum.

The great difficulty which may be encountered in attempting to demonstrate roentgenographically any sinus tract extending from the traction diverticulum is well illustrated in the first case reported in this paper. The edema caused by the inflammatory process is partly responsible. Perhaps a small sinus may be associated with such an esophageal traction diverticulum and thus lead to recurrent abscess formation followed by spontaneous rupture back into the esophagus with subsidence of symptoms.

A small esophagobronchial fistula, especially if it runs in an upward direction from the esophagus so that the bronchial opening is higher, may result in little leakage of esophageal contents into the air passage. Coughing with eating may be slight or may be evoked only by drinking. Position of the patient may influence the tendency of esophageal contents to enter the bronchus. Because of the minimal amount of food or gastric secretion which gets into the lung, the extensive and severe type of pulmonary necrosis seen following large aspirations of gastric contents into the lungs does not usually occur.

Hemorrhage is a frequent symptom in the presence of esophagobronchial fistula. Although the blood is usually coughed up, at times it may be difficult to distinguish between hemoptysis and hematemesis. The bleeding may be frequent and severe. In the first case it was erroneously assumed that the bleeding occurred at the site of ulceration of the calcified lymph node into the bronchus or esophagus. Severe and even fatal hemoptysis may occur from erosion of such a calcific mass into a pulmonary or bronchial vessel. It seems that in most instances of esophagobronchial fistula, however, the bleeding comes from secondary pulmonary abscesses. Both of the cases reported in this paper illus-

trate the difficulties which may be encountered in recognizing the associated disease in the lung. Since it is the paramediastinal portion of the lung which is involved, the pulmonary densities on the roentgenogram merge with the mediastinal shadows and thus may not be recognized as indicating pulmonary disease. If the esophagobronchial fistula communicates with the left lower lobe, the cardiac shadow readily obscures the pulmonary pathology.

Esophagobronchial fistulas have occasionally been treated by the application of a caustic or other irritant to the fistulous openings through an endoscopic approach. According to Clerf, Cooley, and O'Keefe (2), silver nitrate in 25 and 50 per cent solutions was employed unsuccessfully in an attempt to obliterate an esophagobronchial fistula which was later successfully sclerosed by crystals of sodium hydroxide applied at the esophageal end. The chance of successful obliteration of the fistula by cauterization would seem to be influenced by several factors. The thoroughness with which the caustic can be applied, the length of the fistulous tract, the presence of an epithelial lining, and the presence of foreign material such as the remnants of a calcified lymph node would all be of importance. Aside from these factors, such therapy is directed solely toward obliteration of the fistulous tract and ignores any associated pulmonary pathology. If an associated lesion in the lung requires surgical therapy, as frequently happens, operative excision of the fistula with resection of the diseased portion of the lung is certainly the procedure of choice. The involved pulmonary tissue should be excised at the time the fistula is resected. Otherwise serious pulmonary complications may ensue. It should be noted that in the two cases of broncho-esophageal fistula treated successfully by endoscopic cauterization by Clerf there was no evidence of calcified mediastinal lymph nodes or extensive pulmonary suppuration. In the case recorded by Melamed and Zimmerman (3), the esophagobronchial fistula was secondary to an esophageal diverticulum and endoscopic treatment with sodium hydroxide was unsuccessful.

Surgical excision of the fistulous communication with removal of diseased pulmonary tissue is the treatment of choice for esophagobronchial fistula. Coleman and Bunch (1) have reviewed the therapy employed in the reported cases. In view of the relatively few reports of a direct surgical closure of such fistula, and since nonsurgical treatment gave poor results, it is obvious that the benefits of operative correction have not been adequately appreciated in the past. A thorough roentgenographic and bronchoscopic investigation of the lungs should be undertaken before operation in order to obtain maximum information concerning the status of the lungs. Thus the extent of pulmonary resection necessary can be better determined. Gastrostomy is usually not helpful in the preparation of the patient for operation if the fistula communicates with the lower esophagus. Preliminary gastrostomy is occasionally indicated in high fistulas but it should not be done with the expectation that it will result in spontaneous closure of the fistula. Rarely a broncho-esophageal fistula will close without treatment.

SUMMARY

Small esophagobronchial fistulas may be difficult to diagnose because the symptoms may not be characteristic and the roentgenographic evidence of a communication between the air and food passages may be difficult to demonstrate. Severe hemoptyses may occur. Associated pulmonary suppuration often is present in the paramediastinal portion of the lung where it is not readily visualized on roentgenographic studies. The recommended treatment is surgical excision of the fistula with resection of the involved portion of the lung. Two cases illustrating the problems involved are presented in detail.

SUMARIO

Fístula Esofagobronquial Asociada a Hemorragias Graves: Tratamiento por Excisión Quirúrgica y Lobectomía

Las pequeñas fístulas esofagobronquiales pueden resultar difíciles de diagnosticar, por no ser los síntomas típicos y ser difícil descubrir los signos radiográficos de comunicación entre los conductos aéreo y alimenticio. Pude haber hemoptisis intensas. A menudo existe supuración pulmonar asociada en la porción paramediastínica del pulmón, donde no es fácil visualizarla en los estudios roentgenográficos. El tratamiento recomendado consiste en la excisión quirúrgica de la fístula con resección de la porción afectada del pulmón. Preséntanse con todo pormenor dos casos que ilustran los problemas de la situación.

RESUME

Fistule oesophago-bronchique accompagnée d'hémorragies sévères: Traitement par excision chirurgicale et lobectomie

Les fistules oesophago-bronchiques peuvent constituer un diagnostic difficile parce que ses symptômes peuvent n'être pas caractéristiques, et que la preuve d'une communication entre l'air et les voies digestives est parfois difficile à établir par la radiographie. Des hémoptysies importantes peuvent être observées. La suppuration au niveau du segment paramédiastinal du poumon y est souvent associée, elle n'est pas facile à déceler sur les radiographies. Le traitement recommandé est l'excision chirurgicale de la fistule avec résection du segment pulmonaire intéressé. Deux cas illustrant ces conditions sont présentés en détail.

REFERENCES

(1) Coleman, F. P., and Bunch, G. H., Jr.: Acquired nonmalignant esophagotracheobronchial fistula, J. Thoracic Surg., 1950, *19*, 542.

(2) Clerf, L. H., Cooley, E. E., and O'Keefe, J. J.: Esophagobronchial fistula, Surg., Gynec. & Obst., 1943, *77*, 615.

(3) Melamed, A., and Zimmerman, B. M.: Esophagobronchial fistula through an esophageal diverticulum, Am. J. Roentgenol., 1946, *55*, 20.

TUBERCULOMA OF THE CEREBELLOPONTINE ANGLE SIMULATING ACOUSTIC NEUROMA[1]

CHARLES W. ELKINS AND FRANK J. RACK

(Received for publication September 21, 1950)

The diagnosis of lesions in the cerebellopontine angle can be made quite readily in most instances by the characteristic progressive signs and symptoms. In differential diagnosis consideration should be given to the possible presence of acoustic neuroma, fibroma of the auditory nerve, pearly tumor, glioma of the cerebellum or brain stem, meningioma, tumors of the fourth ventricle, local inflammatory or vascular lesions of the inner ear, and Meniere's disease.

Tuberculoma developing in the cerebellopontine angle and simulating acoustic neuroma is rare, and only two references to such a lesion could be found (1, 2). Accordingly, such a case of tuberculoma recently studied in this hospital is reported.

CASE REPORT

J. M. (# 261084), a 60-year-old white male, was admitted to Cleveland City Hospital on September 2, 1948 with Pott's disease of the lumbar vertebrae. He had complained of pain in the lower lumbar region for thirteen months with radiation of the pain to the left iliac crest for three months.

Past history: The patient had been hospitalized at Cleveland City Hospital in 1938 because of right upper lobe pneumonia, in 1944 because of bronchopneumonia, and for ten months in 1945 because of minimal pulmonary tuberculosis with effusion. A right low-thigh amputation had been done in 1934 because of gangrene secondary to a compound fracture.

Examination on admission revealed tenderness over the back in the midline over the spines of the fourth and fifth lumbar vertebrae. A roentgenogram of the chest revealed healed minimal pulmonary tuberculosis in the right first anterior interspace. Roentgenograms of the lumbar spine revealed bone destruction and collapse of the bodies of the fourth and fifth lumbar vertebrae. Lumbar puncture yielded clear cerebrospinal fluid with normal pressures, no cells, and 90 mg. of protein per 100 cc.

Hospital course: A body cast was applied and the patient was treated with bed rest for the next ten months. On June 16, 1949, under gas-oxygen-ether anesthesia, arthrodesis of the lumbar spines was carried out. Following this procedure, the patient was again placed in a plaster cast and kept on bed rest.

On September 10, 1949, the patient began to complain of a loud roaring noise in both ears, more marked on the left and more severe in the upright position. He also noted some impairment of hearing on the left. On September 16, paresthesias and hypesthesias developed in the left supraorbital and maxillary regions, and by September 20 there was complete deafness on the left. Definite weakness of the left facial muscles was also noted. As the patient was still in a plaster cast, it was deemed advisable to postpone operation for what seemed to be a typical acoustic neuroma. During the next month there was a gradual improvement in the sensory changes over the forehead and mouth and considerable decrease in the facial weakness and roaring in the ear.

On November 23, the patient was transferred to the neurosurgical service for surgical exploration. Positive findings at that time included: lateral and rotatory nystagmus of the left eye, diminished corneal reflex, complete loss of hearing and labyrinthine function on the left, diminished touch perception over the peripheral distribution of the trigeminal nerve

[1] From the Division of Neurosurgery, Department of Surgery of Cleveland City Hospital, and the School of Medicine, Western Reserve University.

on the left, and paresis of the left facial muscles and weakness of the left lateral rectus. There was no papilledema. Lumbar puncture was not performed because of difficulties secondary to arthrodesis of the lumbar spine. Roentgenograms of the skull in Stenver's position failed to demonstrate abnormalities of the internal auditory meati and no evidence of bone destruction of the petrous ridges was found.

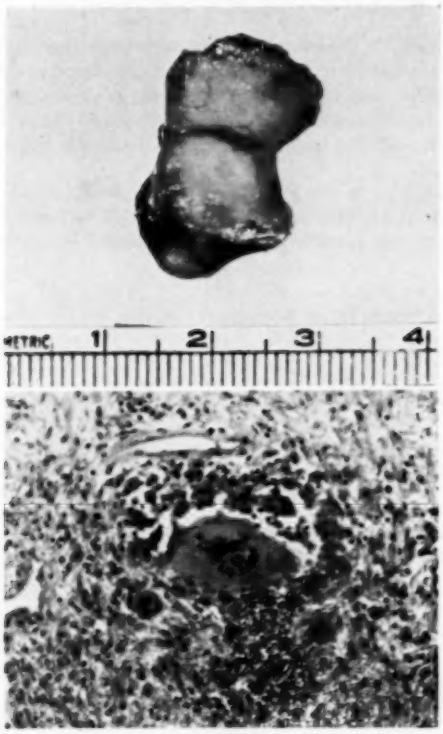


FIG. 1. (Top) Cut section showing tuberculoma

FIG. 2. (Bottom) Photomicrograph of tuberculoma showing caseation with giant cell, epithelioid cells, and lymphocytes.

Operative note: A left suboccipital exploration was performed on December 9. A tissue mass was found to be attached to both the left eighth and fifth nerves and was situated in close proximity to the pons. This tumor was rather readily dissected from the triangle formed by the two nerves and the pons. It was spherical and had an approximate diameter of 3 cm.

On December 12, 1949, the administration of streptomycin was started and 0.5 gm. was given twice daily for forty days.

Pathology: The fresh specimen consisted of an irregular nodular soft piece of tissue measuring approximately 3.5 cm. in diameter. The external surface was pink, mottled with gray. It was sectioned with decreased resistance to reveal gray, soft, homogeneous surfaces (figure 1).

Microscopic examination of the sections revealed conglomerate tubercles with central caseation. Several typical giant cells were present along the margin of caseation. Epithelioid cells and numerous lymphocytes were in the peripheral zone (figure 2). Acid-fast stains demonstrated the presence of acid-fast bacilli in many areas.

Ascites was present on January 27, 1950, and the following day 4,100 cc. of fluid were removed from the abdomen. During the next ten days the patient's condition deteriorated and he died on February 12, 1950. Permission for post-mortem examination was not obtained.

DISCUSSION

The progression of signs and symptoms in this patient was fairly typical of that seen in the slow-growing acoustic neuroma. Three characteristic stages in the growth of an acoustic neuroma are described, and this grouping is made according to inroads made on contiguous structures (3).

The first stage consists of eighth nerve disturbances, and in this patient loud roaring noises along with impairment of hearing were the first symptoms noted. The second stage usually consists of paresthesias of the face along the peripheral distribution of the trigeminal nerve followed by some facial nerve involvement. These signs and symptoms were also noted shortly after the eighth nerve disturbances. The third phase in the development of an acoustic neuroma results from the displacement and compression of the pons and medulla with obstruction of the ventricular system and increased intracranial pressure. In the present case, the patient was subjected to surgery before the advent of this phase.

At operation the tumor was thought to be a tuberculoma and was excised. However, this procedure failed to produce resolution of the signs and symptoms. From the subsequent development of ascites and the fairly rapid downhill course of the patient, it was assumed that the patient had generalized tuberculosis and that the failure of resolution was probably due to additional intracranial involvement.

SUMMARY

A case is reported in which a tuberculoma of the cerebellopontine angle closely simulated an acoustic neuroma in a 60-year-old white male.

SUMARIO

Tuberculoma del Angulo Cerebelo-Pontil Simulando Neuroma Acústico

En el caso comunicado, un tuberculoma del ángulo cerebelo-pontil en un varón blanco de 60 años simulaba íntimamente un neuroma del auditivo.

RESUME

Tuberculome de l'angle cérébello-pontin simulant un névrome du nerf acoustique

Chez un homme de 60 ans, de race blanche, on a observé un tuberculome de l'angle cérebello-pontin qui pouvait être confondu avec un névrome du nerf acoustique.

REFERENCES

(1) ALQUIER, L.: Volumineux tubercle caseifie de la callatte protuberantielle étude anatomo-clinique, Rev. Neurol., 1906, *14*, 406.

(2) ROSENTHAL, M.: Klinik der Nervenkrankheiten, 1875, p. 199.

(3) DANDY, W. E.: Lewis' Practice of Surgery, 1944, W. F. Prior Co., Hagerstown, Maryland, Vol. XII, Chapter 1, p. 521.

AMERICAN TRUDEAU SOCIETY

Medical Section of the National Tuberculosis Association

Notes

The Committee on Medical Research of the American Trudeau Society a nd its subcommittees met in New York City on November 14, 15, 16, and 17, 1950. At the meeting on November 16, recipients of research grants from the Society met with the Committee and made verbal reports on the progress of their investigations. There was spirited discussion, and all present felt the meeting was stimulating and profitable. The annual joint meetings of grantees and members of the Committee now form an important feature of the program of the American Trudeau Society, and it is believed the discussions at these meetings are reflected in broader outlook and greater accomplishment by those receiving financial support from the Society.

On the following day, November 17, the Committee considered applications for renewal of projects and new applications, and made recommendations for the 1951–1952 fiscal year for consideration by the Board of Directors of the National Tuberculosis Association in February 1951.

At the present time 31 research grants are financed by the Society and 12 Fellowships are in operation.

The following postgraduate courses in pulmonary disease have been held or are scheduled for the 1950-1951 fiscal year:

Date	*Place*	*Sponsor*	*Chairman*
May 15–19, 1950	Pittsburgh, Pa.	University of Pittsburgh	C. Howard Marcy
Week of March 26, 1951	Boston, Mass.	Harvard Medical School Tufts College Medical School Boston University Medical School	Dr. dward J. Welch 1101 Beacon Street Brookline, Mass.
March 26–31, 1951	Milwaukee, Wis.	ATS and Marquette University School of Medicine	Dr. Richard P. Jahn 1705 West Wisconsin Ave. Milwaukee, Wis.
March 29 April 5 12 19	Albany, N. Y.	ATS and Albany Medical College	Dr. John K. Neneely, Jr. Union University Albany Medical College Albany, New York

A course in broncho-esophagology and peroral endoscopy will be given at Temple University, Philadelphia, Pa., March 4 to 16, 1951. Further information and application blanks are obtainable through Dr. Chevalier L. Jackson, 3401 North Broad Street, Philadelphia 40, Pa.

THE AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

Edited by LAWRENCE B. HOBSON

VOLUME 63 FEBRUARY, 1951 ABST. NO. 2

CLINICAL STUDIES, TUBERCULOSIS

Tuberculosis in the Aged.—Of 1,329 patients discharged from Homer Folks Tuberculosis Hospital over a nine-year period, 226 (17 per cent) were 50 years of age or older at the time of their admission. Of these, 64.6 per cent had far advanced, 22.6 per cent had moderately advanced, and 12.8 per cent had minimal tuberculosis. In the far advanced group, 73 per cent died within one year of hospital admission. Of the 44 patients alive at the end of the study period, 26 had active, 6 had quiescent, 3 had apparently arrested, and 9 had arrested disease. On the basis of experience in this group it is believed that collapse therapy should be employed more frequently in the treatment of aged patients, but these cases must be chosen with the greatest of care. Thoracoplasty was performed four times in the far advanced group and was of clinical benefit in all cases.—*Problems presented by pulmonary tuberculosis in patients over fifty, E. L. Leech, Ann. Int. Med., August, 1950, 33: 321.*—(*T. H. Noehren*)

Primary Pleurisy With Effusion.—The diagnosis of primary or idiopathic pleurisy with effusion can only be made when adequate history, clinical and laboratory examinations, and radiologic investigation exclude any underlying parenchymal lung disease. In a series of 78 cases, there was no previous history suggesting tuberculosis and chest roentgenograms taken at the time of enlistment shortly before the onset of pleurisy were negative. The series may be divided into two groups: 40 patients had positive pleural fluid cultures for tubercle bacilli, and 38 had negative pleural fluid cultures. The symptoms, clinical findings, and course of the disease were essentially the same whether the pleural fluid cultures were positive or negative for tubercle bacilli. There were differences in degree, however, inasmuch as fluid appeared sooner after the onset of symptoms and persisted longer in the positive group. The incidence of subsequent tuberculosis was essentially the same, 44 per cent and 42 per cent in the positive and negative groups, respectively. However, the disease manifested itself after a shorter interval in the positive culture group and was of a more serious and extensive nature. Primary or idiopathic pleurisy with effusion is frequently an early or primary manifestation of tuberculous infection. The incidence of other later manifestations of tuberculosis is also high.—*Primary or idiopathic pleurisy with effusion, W. A. Oille, Canad. M. A. J., August, 1950, 63: 112.*—(*T. H. Noehren*)

Cultures of Female Genital Tuberculosis.—Tuberculosis of the endometrium has been diagnosed by biopsy and Moriyo has reported specific roentgenographic changes in tuberculous salpingitis. A successful method of culturing tubercle bacilli from the vagina would offer advantages over either procedure. The author has employed, for this purpose, the Oka-Katakura phosphate-ajinomoto-egg medium. During the intermenstrual period, vaginal contents were removed and digested with 5 to 10 times their volume of 5 per cent sulfuric acid, containing 0.02 per cent of 3,6-diamino-10-methyl-acridium chloride. The centrifuged sediment was then cultured. During menstruation, the vaginal contents were washed out with 18 cc. of a sterile solution of 0.01 per cent saponin and 0.25 per cent calcium chloride. The centrifuged sediment was ground, digested, and cultured. Using these methods, 18 patients with normal menstruation were examined throughout the menstrual cycle. All yielded positive cultures, the best growth being obtained from specimens col-

lected during the first and second days of the menstrual flow. Of the 18, positive cultures could be obtained in 8 only during menstruation and the five days immediately before the flow. Of 6 patients with oligomenorrhea, one gave abundant cultures and 5 were positive only during the premenstrual and menstrual periods. The latter included 2 cases of proved salpingitis without endometrial involvement. Of 4 amenorrheic patients, 3 with far advanced pulmonary tuberculosis yielded abundant vaginal cultures. The remaining patient with long-standing, quiescent genital tuberculosis had only a few tubercle bacilli culturable from the vagina. It thus seems that vaginal cultures made on the two days preceding menstruation and on the first two days of menstruation afford a sensitive and simple method for diagnosing genital tuberculosis in women.—*Tubercle bacilli in vagina in the tuberculosis of female genitals, S. Furuhashi, Tohoku J. Exper. Med., May, 1950, 52: 157.*—(*L. B. Hobson*)

Spontaneous Hemopneumothorax.—Hemothorax, though rare, is a potential complication in every case of spontaneous pneumothorax. In many cases there is an interval of several hours to days between the initial symptoms and the signs and symptoms of intrathoracic bleeding. Of 2 cases reported, one was fatal. The other required 4,000 cc. of blood intravenously, while 4,900 cc. of bloody fluid were evacuated from the pleural space. It is believed that blood therapy is indicated since persistent shock, clinical or subclinical, is much more dangerous than the doubtful possibility of starting renewed bleeding as a result of the transfusion therapy. More widespread awareness of the problem and its relation to simple pneumothorax would undoubtedly decrease the mortality, since the loss of time in the institution of treatment may be disastrous.—*Spontaneous hemopneumothorax: Report of two cases, D. B. Arst, W. J. Lahey, & P. Kunkel, Ann. Int. Med., September, 1950, 33: 718.*—(*T. H. Noehren*)

Streptokinase for Hemothorax.—A patient was receiving artificial pneumothorax for tuberculosis when a massive hemothorax appeared. Aspiration soon became impossible because of clots. Streptokinase was introduced intrapleurally twice. The clots were liquefied so that aspiration could be resumed. Later, the pneumothorax was continued.—*Massive haemothorax in artificial pneumothorax treated with streptokinase, R. G. Gould & J. T. Harold, Brit. J. Tuberc., July, 1950, 44: 77.*—(*A. G. Cohen*)

Open Healing of Cavities.—Examinations of gastric and bronchial washings are not sufficient to prove open healing of a cavity. The absence of tubercle bacilli must be demonstrated in the cavitary secretions obtained by intracavitary aspiration and lavage. Three hundred endocavitary examinations have shown this method to be innocuous and usually easy to carry out in cavities with a diameter of 2 cm. and more. The proof of bronchial occlusion is obtained by intracavitary injections of methylene blue or lipiodol. It is considered worthwhile to carry out these procedures in order to prevent unnecessarily prolonged hospitalization of certain patients with roentgenographic evidence of cavitation. —*Cavernes exclues et guéries: Les elements du diagnostic, G. Roche & I. Vonjean, Rev. de la tuberc., 1950, 14: 510.*—(*V. Leites*)

Thoracoplasty with Plombage.—An operation was devised which is a modification of an ordinary thoracoplasty but in which the relaxation of the lung is maintained by the insertion of plastic spheres. The third rib and most of the second are respected. The lung is stripped as far down as the fifth to ninth rib according to the extent of the lesion. The plastic spheres are packed loosely into the space. The initial cases were those suited for standard thoracoplasty. Later, poor-risk cases were included. In a series of 125 operations, complications included atelectasis and spread, 5 each; effusion into space, 18; and space infection, 3. Three deaths occurred.—*Thoracoplasty with plombage: A review of the early results in 125 cases, B. G. B. Lucas & W. P. Cleveland, Thorax, September, 1950, 5: 248.*—(*A. G. Cohen*)

Tuberculin with ACTH and Cortisone.—At least two alterations in the host are produced by cortisone and adrenocorticotrophic hormone (ACTH): (*1*) The lymphoid system and, by implication, its immunological functions are profoundly affected; (*2*) many biochemical phenomena are equally altered. Recent studies suggest that ACTH may abolish anaphylactic allergy. The present report indicates that alterations in the tuberculin type of allergy may also be seen during ACTH and cortisone treatment. Repeated skin tests with PPD and beta hemolytic *Streptococcus* vaccine (BHS) were performed on 34 patients receiving either ACTH or cortisone or both. The PPD was used in the lowest standard strength showing a positive reaction. The BHS vaccine contained approximately 9×10^9 dead organisms per ml. and was given intradermally concomitantly with the PPD tests. Eight patients received skin tests of histamine phosphate. The histamine reaction was used as the prototype of immediate hypersensitivity in contrast to the PPD and BHS reactions which are reactions of the delayed type. Approximately one-half of the patients receiving the new hormones had rheumatoid arthritis. Twelve rheumatoid patients receiving neither ACTH nor cortisone served as controls. The PPD reaction was obliterated in 13; and the BHS reaction, in 19 of the 34 treated patients. In 7 of the 34, initial tests with tuberculin were not available and 8 of the group received no initial BHS test. The time of obliteration of the reactions was from three to thirty days and was affected by the patient's initial degree of sensitivity, the dosage of hormone, and the duration of treatment. In this study any erythema or induration occurring after the tenth hour was considered significant. The most readily altered phase of the tuberculin type of reaction was necrosis. The prevention of induration was more difficult to achieve but sufficient therapy completely abolished even the erythema. Those patients in whom the reactions were not obliterated showed a significant alteration of induration and erythema in one or both intradermal tests. Retesting usually showed a return to positivity seven to twenty-eight days after completion of hormone treatment. Delayed reactions (PPD and BHS) observed in the control patients during the same period showed wide variations in induration and erythema from week to week. Normal histamine reactions were observed in treated and untreated patients.—*The ability of ACTH and cortisone to alter delayed type bacterial sensitivity, J. B. Long & C. B. Favour, Bull., Johns Hopkins Hosp., September, 1950, 87: 186.*—*(J. S. Woolley)*

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Disseminated Coccidioidomycosis.—A young white woman, while in an endemic area for *Coccidioides immitis*, conceived and delivered a normal baby who has remained healthy. Two months later a granulomatous but asymptomatic coccidioidal endometritis was discovered without a preceding history of respiratory infection or cutaneous lesion, at which time roentgenographic examination of the chest was normal. Three months later symptoms of generalized disease developed. Pulmonary lesions did not appear until nearly two years after the establishment of uterine infections. During this time repeated coccidioidin skin tests were negative, but a facial cutaneous coccidioidal granuloma appeared, followed by marked eosinophilia. Two and one-half years from its onset, the disease became fulminating and terminated in death despite the use of protoanemonin which *in vitro* prevented the growth of the fungus isolated from the patient's blood. It is suggested that the uterus may have been the portal of entry of infection in this patient (Authors' summary). —*Disseminated coccidioidomycosis, N. J. Conan, Jr. & G. A. Hyman, Am. J. Med., September, 1950, 9: 408.*—*(T. H. Noehren)*

Syphilis of the Lung.—Criteria for the clinical diagnosis of syphilis of the lung have been established as follows: (*1*) history of syphilis, (*2*) signs and symptoms of pulmonary disease, (*3*) radiographic evidence of pulmonary disease, (*4*) presence of associated syphilitic lesions in other organs, (*5*) positive serologic test for syphilis, (*6*) demonstration of *Treponema pallidum*, (7) therapeutic test, and

(*5*) exclusion of other forms of pulmonary disease. The case of a 22-year-old single white woman is presented in whom roentgenograms of the chest showed a circumscribed area of density, more opaque centrally and located in the left upper lung field. Fluoroscopy revealed this area to be continuous with what appeared to be enlarged posterior mediastinal lymph nodes. Bronchoscopy revealed inflammation of the mucosa of the left main stem bronchus, with 33 per cent stenosis. Treatment consisted of penicillin and bismuth subsalicylate, with resultant complete regression of the pulmonary lesion. The blood serology was positive but specific bacteriologic evidence of syphilis was not found.—*The criteria for clinical diagnosis of syphilis of the lung; with report of a case, B. F. Royce, Ann. Int. Med., September, 1950, 33: 700.*—(*T. H. Noehren*)

Mucor-Mycosis of the Lung.—Molds are fungi that belong to one of 3 main groups, the prototype genera of which are *Penicillium*, *Aspergillus*, and *Mucor*. Aside from their occasional allergenic action, they can generally be regarded as saprophytic or parasitic on other plants. Some authors believe that massive inhalation of mold spores can cause a primary mold infection of the lung, but such cases are rare. *Aspergillus* is more often implicated than *Mucor*. The latter has been reported only once before in this country. From the majority of carefully investigated cases of mold infections, however, it seems that a predisposing condition such as diabetes, pneumonia, infarction, or other local primary disease generally exists. The growth of the mold in lung tissue causes necrosis which may proceed to odorless gangrene or to resultant fibrosis. Calcific particles may be found in the lesion. The authors' case of this type of *Mucor-mycosis* was cured by excision of the lesion.—*Mucor-mycosis of the lung, J. D. Murphy & S. Bornstein, Ann. Int. Med., August, 1950, 33: 442.*—(*T. H. Noehren*)

Hydatid Disease of the Lungs.—Three different types of hydatid pulmonary disease have been treated medically. (*1*) In cases of suppurative pulmonary hydatid cysts, retained membranes act as foreign bodies except in rare instances of complete encystment or calcification. The suppuration is treated by the transthoracic injection of antibiotics chosen for the organisms identified in aspirated material. The complete expulsion of the membrane is essential to end the suppuration. This is achieved by the mechanical effect of severe bouts of coughing associated with the injections. The flow of fluid toward the dilated bronchi carries along fragments of endocyst which have been detached and broken up by the cough, by proteolytic enzymes, and by the injecting needle. Bronchoscopic suction is ineffective. Following expulsion of the parasitic cyst, infection subsides and healing occurs rapidly without residual pulmonary damage and only insignificant pleural sequelae. (*2*) In cases in which the cysts have ruptured spontaneously, treatment is directed at removing the retained parasitic lining membrane. This is achieved over several months by the injection of a solution of pepsin and hydrochloric acid which digests the membrane and allows it to be expectorated. (*3*) The treatment of clean, noninfected, closed, hydatid cysts requires the desensitization of the patient by injections of increasing doses of hydatid fluid and its antigen. The cyst is then fixed to the chest wall by inducing a pneumothorax and producing an obliterative pleurisy by means of irritants. When this is achieved the cyst is punctured and the fluid is partially aspirated. Sterilization of the cyst's contents is achieved by the introduction of formalin, and the cyst is evacuated. Following evacuation, suppuration either develops naturally or is induced; as an alternative, digesting substances may be introduced. Treatment is then similar to those cases in which infection pre-existed. The advantages of this method are that it may be completely effective, it is nontraumatic, it leaves no permanent bronchopulmonary damage, it eliminates an operative risk, it may be carried out on an ambulatory basis, and it is no bar to subsequent surgery in the event of failure.—*Medical treatment of hydatid cysts of the lung, M. R. Castex &*

E. L. Capdehorn, Brit. M. J., September 9, 1950, No. 4679: 604.—(E. A. Riley)

Pulmonary Insufficiency in Cystic Disease.—The authors propose a classification of large pulmonary air cysts or bullae based upon physiological studies in 16 cases. These are divided into 3 groups: (*1*) The cyst communicates freely with the bronchial tree; the remainder of the lung is normal. (*2*) The communication with the bronchial tree is intermittent or poor; the remainder of the lung is normal. (*3*) Generalized emphysema: In group (*1*), there is a physiological dead space but no interference with function; surgical intervention is optional. In group (*2*), varying degrees of pulmonary insufficiency develop. There is considerable interference with the bellows action of the chest by the tension cyst; surgery is mandatory. Group (*3*) is subdivided according to the presence or absence of alveolorespiratory insufficiency in addition to ventilatory insufficiency. In the first instance, surgery may be helpful and well tolerated; in the second, resection may be dangerous.—*Pulmonary insufficiency: IV. A study of 16 cases of large pulmonary air cysts or bullae, E. De F. Baldwin, K. A. Harden, D. G. Greene, A. Cournand, & D. W. Richards, Jr., Medicine, September, 1950, 29: 169.—(A. G. Cohen)*

Pulmonary Arteritis with Congenital Heart Disease.—In a case of congenital heart disease of the Eisenmenger type, necrotizing arteritis (periarteritis nodosa) was limited to the pulmonary arteries. Such a limitation of the arterial involvement has not previously been reported. The patient was an 11-year-old boy who was hospitalized with symptoms suggesting a severe pneumonia. A congenital cardiac lesion had been recognized at birth. A roentgenogram of the chest showed soft infiltrations 1 to 5 mm. in size in both lung fields, and a tentative diagnosis of miliary tuberculosis was made. The boy lived only 6 hours. At autopsy there was a partial dextroposition of the aorta with a defect in the membranous part of the interventricular septum (Eisenmenger complex), moderate chronic mitral endocarditis and slight chronic endocarditis of the aortic valve, moderate pulmonary arteriosclerosis and advanced pulmonary arteriolosclerosis, advanced necrotizing pulmonary arteritis of the tertiary radicles and moderate necrotising pulmonary arteriolitis, moderate chronic bronchitis and bronchiolitis with excess mucus formation, and moderate emphysema of the lungs. Pulmonary arterial pressures are increased in every instance of Eisenmenger's complex. An elevation of pulmonary hydrostatic pressure is postulated, therefore, in the present case, and the pulmonary arteriolosclerosis could be the anatomical expression of this elevated pressure. This might explain also the limitation of the arteritis to the pulmonary arteries.—*Necrotizing pulmonary arteritis occurring with congenital heart disease (Eisenmenger complex), J. W. Old & W. O. Russell, Am. J. Path., September, 1950, 26: 789.—(J. S. Woolley)*

Collateral Arterial Pulmonary Circulation.—In attempting to increase the arterial circulation to the lungs in patients with Fallot's tetralogy or pure pulmonic stenosis, an occasional patient is encountered in whom the standard operations are not feasible. Barret and Daley reported a case where a long dissection of the lung root and superior mediastinum was carried out; the operation was abandoned when the Blalock anastomosis could not be completed. Three months later the child was remarkably improved, with a marked reduction in cyanosis. This was attributed to the development of vascular adhesions between the lung and the parietes across the areas denuded of pleura. Pleural stripping was then used as a definitive operation in 6 cases, with encouraging results. In the present investigation 3 dogs were used to determine if adhesions carrying blood vessels could be created. The dogs were subjected to 3 operations each: (*1*) The main pulmonary artery to one lung was ligated. (*2*) After a lapse of three months, stripping of the mediastinal (lung root) and parietal pleura was carried out on the side of the previous operation.

(5) Three or more months after the second procedure, the opposite side of the thorax was opened and the main stem bronchus to the normal lung occluded to determine if life could be maintained by the lung on the side of the pulmonary artery ligation. The animal was then sacrificed and the vessels of the lung injected either through the intercostals alone, after division of the hilar structures, or through the intercostal and bronchial vessels together. Two animals developed good intrapleural adhesions and one survived occlusion of the opposite main stem bronchus for fifty minutes. Injections in these 2 animals showed dye in the pulmonary artery and obvious communication with the systemic circulation through new blood vessels traversing the intrapleural adhesions. In the third animal, the areas of denudation had become repleuralized so that no adhesions were present. Postoperative pneumothorax was presumed to have allowed healing before adherence took place. It was concluded that small precapillary anastomoses exist within the lung between the bronchial arteries and the pulmonary arteries and that under sufficient demand, as after pulmonary artery ligation, blood from collateral vessels may enter the pulmonary circulation. This mechanism for supplying systemic arterial blood to the lung capillaries has been called the "bronchopulmonary shunt."—*The collateral circulation to the lungs, F. B. Cockett & C. C. N. Vass, Brit. J. Surg., July, 1950, 38: 97.—(M. G. Carter)*

Nodular Pulmonary Ossification.—There are 2 forms of pulmonary ossification, the branching form, which is the commoner; and the nodular form, which is much rarer. The latter usually appears early in adult life, most frequently in the thirties, as often in men as in women. The lesions are bilateral and usually are located in the lung bases. They often appear some years prior to the development of cardiac insufficiency. Often in mitral disease the nodules develop simultaneously with other evidences of stasis such as heart failure cells and iron deposits. They appear in the intra-alveolar septa, especially in connection with the fibrinoid necrosis of the media and thickening of the vascular wall which so often forms part of the picture in subacute rheumatic polyserositis. The clinical history and the presence of severe stasis helps to differentiate them from tuberculous lesions.—*Ossification pulmonaire nodulaire disséminée dans un cas de maladie mitral, G. Tverdy, Rev. belge path., December, 1949, 19: 321.—(A. T. Laird)*

Hypertrophic Osteoarthropathy.—A severe and unusual case of extensive hypertrophic pulmonary osteoarthropathy secondary to squamous cell carcinoma of the lung is presented. Following surgical removal of the carcinoma, the bone lesions and clubbing of the fingers rapidly regressed. Gynecomastia disappeared simultaneously, suggesting an endocrine factor in the pathogenesis of this condition. In previous cases, gynecomastia and acromegalic changes have been reported with an associated hyperplasia of the eosinophilic cells of the anterior pituitary gland. That the thyroid gland may also play some role in the clubbing of the fingers is suggested by the reported occurrence of digital tufting in cases of exophthalmic goiter that develop postoperative myxedema. Since clubbing rarely and gynecomastia frequently are encountered in biliary cirrhosis, the theory is held that the latter is contingent upon the inability of the liver to conjugate estrogens. The fact that both the liver and the lung have two afferent blood supplies, venous and arterial, suggests that this phenomenon of pulmonary osteoarthropathy may be dependent upon an arteriovenous shunt. The conclusion can be drawn that either the lesion itself stimulates osseous proliferation or it elaborates a substance that induces the effect by acting through the anterior pituitary gland.—*Severe hypertrophic pulmonary osteoarthropathy, J. R. Fischl, Am. J. Roentgenol., July, 1950, 64: 42.—(T. H. Noehren)*

Oxygen Therapy.—A 60-year-old man was treated with digitalis, a mercurial diuretic, and oxygen therapy for emphysema and right heart failure. The patient became comatose

whenever oxygen was administered; when it was withdrawn he regained consciousness. The patient died after three days. Autopsy confirmed the clinical diagnosis. Careful observations on 65 additional patients with chronic anoxemia revealed mental changes in 8 patients. There is no doubt that some chronically anoxemic patients may become somnolent or even comatose during the administration of 100 per cent oxygen. The possible mechanisms responsible for these reactions are (*1*) carbon dioxide narcosis; (*2*) cerebral vasospasm; (*3*) reflex depression of the cerebral cortex by high oxygen tension; (*4*) increased cerebrospinal fluid pressure; and (*5*) direct depression of the cerebral cortex by high oxygen tension.—*Mental changes occurring in chronically anoxemic patients during oxygen therapy, J. H. Comroe, Jr., E. R. Bahnson, & E. O. Coates, Jr., J.A.M.A., July 22, 1950, 143: 1044.*—(*H. Abeles*)

Aplasia of the Lung.—Aplasia of the lung is usually asymptomatic. It occurs in men more frequently than in women by a ratio of 3 to 2. It is seen three times as often on the left side as on the right. Cases diagnosed are usually the result of an accidental finding during physical examination or roentgenographic study in cases of extrapulmonary disease. Two cases of aplasia of the lung diagnosed during life are presented, bringing to 18 cases the total number which have been diagnosed during life. In Case 1 the findings were further corroborated by angiocardiographic demonstration of a single pulmonary artery. This is believed to be the first time that such a study has been undertaken, since there is no previous report in the literature. Case 2 is in no way unusual except that it is a proved case of aplasia of the lung diagnosed during life. It does show a congenital defect of the spine with hemivertebra of the dorsal spine, an occurrence which has previously been reported by Gartside in England in 1943 and by Ferguson and Neuhauser in 1944 in this country. It is thought that with further use of the mass survey method in chest roentgenography many heretofore undiagnosed cases of aplasia of the lung will be recorded (Authors' summary).—*Aplasia of the lung with angiocardiographic demonstration of anomalous pulmonary circulation, M. D. Ingram, Jr., G. W. Hudson, & T. J. Davis, Am. J. Roentgenol., September, 1950, 64: 409.*—(*T. H. Noehren*)

Pulmonary Embolism by Amniotic Fluid.—The authors report 3 cases of pulmonary embolism due to amniotic fluid, and review the literature. The patients are usually older multiparae, many of whom are beyond term. The prenatal course is uneventful, and there are no complications before labor. Characteristically, hard, violent, or tetanoid uterine contractions appear during or shortly after labor. The first symptom is chilliness which is followed by a fall in blood pressure to shock levels. The patients become restless and anxious, dyspnea and cyanosis appear, response becomes poor, and death ensues in a matter of minutes or hours. The fetus is often stillborn or dies shortly after birth. Pathologically, no gross emboli are seen in the mother. Microscopically, it is possible to demonstrate elements characteristic of amniotic fluid and meconium in the small pulmonary arterioles and capillaries. In less than 50 per cent of cases, a tear is found in the uterus or cervix. The portal of entry is undoubtedly an abnormal communication between the uterine cavity and its vessels. The condition is very rare.—*Maternal pulmonary embolism by amniotic fluid, G. C. Mallory, W. Blackburn, H. J. Sparling, & D. A. Nickerson, New England J. Med., October 19, 1950, 243: 583.*—(*A. G. Cohen*)

Atelectasis from Intravenous Fluids.—Congestive atelectasis has been described as a complete absence of air from the alveoli due to a maximal dilation of the lung capillaries. Macroscopically, the condition simulates hemorrhage, but inflation of the lung causes the airless parts to disappear. The symptoms differ from obstructive atelectasis in only a few respects. The cyanosis clears with difficulty in congestive atelectasis, the mediastinum does not shift, although the involvement was al-

ways bilateral, the lesions cannot be noted roentgenographically, and aspiration is not effective. Congestive atelectasis is more likely a cause than a result of shock. Rapid decompression has been said to be the cause, but it was not etiologic in more than 20 of the authors' cases. Physical injury, anaphylactoid reactions, pre-existing shock, and excessive or rapid intravenous infusions appeared to be contributory; only one patient recovered. Digitalis, oxygen, bronchoscopic aspiration, phlebotomy, deep breathing with 5 per cent carbon dioxide, and oxygen under positive pressure were almost entirely ineffective. It seemed impossible to discover the etiology without further experimentation and the effects of rapid infusion of fluids into lightly anesthetized normal dogs and dogs with "tourniquet shock" were studied. The etiology was not entirely clarified, but it was shown that several of the results of infusion are similar to those of acute pulmonocardiac failure.—*Congestive atelectasis—a complication of the intravenous infusion of fluids, M. T. Jenkins, R. F. Jones, B. Wilson, & C. A. Moyer, Ann. Surg., September, 1950, 132: 327.—(W. H. Oatway, Jr.)*

Pneumoperitoneum for Emphysema.—The following criteria were used in the selection of cases of pulmonary emphysema for therapeutic pneumoperitoneum: (*1*) pulmonary insufficiency with dyspnea which prevented work, (*2*) cor pulmonale absent or minimal, and (*3*) pulmonary infection adequately treated. Each of the 22 selected patients received a complete work-up which included functional studies. The chief symptom was severe dyspnea; cough and expectoration were prominent. The temperature and pulse rate were normal. The thorax was barrel-shaped, and rhonchi and rales were heard. The arm-to-tongue circulation time using magnesium sulfate was 12 to 20 seconds. Bronchoscopic examination showed pale mucosae with loss of bronchial elasticity. The initial insufflation of air was 700 to 1,000 cc. Refills of 500 to 1,000 cc. were given at two-day intervals and then every two weeks. The diaphragmatic rise was less than that required in cases of tuberculosis. Improvement was noted in 13 cases; in 10, this was marked, the maximal improvement usually being achieved in six to eight weeks. There was a reduction in the dyspnea and increase in the tussive force, so that expectoration was facilitated. No patient was made worse. In emphysema, the amount of residual air is increased at the expense of the vital capacity; pneumoperitoneum corrected this shift. The maximal breathing capacity, which averaged only 29 liters per minute before treatment, was increased to 37. The walking-dyspnea index was reduced. Patients who showed a slight increase in maximal breathing capacity after bronchodilator drugs administered as an aerosol showed a much greater increase after pneumoperitoneum.—*Pneumoperitoneum in the treatment of pulmonary emphysema, M. G. Carter, E. A. Gaensler, & A. Kyllonen, New England J. Med., October 12, 1950, 243: 519.—(A. G. Cohen)*

Pneumoperitoneum for Emphysema.—Five of 7 patients with pulmonary emphysema were greatly relieved by therapeutic pneumoperitoneum; the other 2 patients with severe emphysema were unable to tolerate the air because of abdominal pain. Improved respiratory function and a marked reduction in the number and severity of asthmatic episodes were noted. It is believed that limitation of diaphragmatic movement in cases of emphysema is due to the fact that the intrapleural and intra-abdominal pressures approach one another. Introduction of air into the abdomen raises the diaphragm, increases the intra-abdominal pressure, and allows better diaphragmatic function. Studies showed that the increased vital capacity and diaphragmatic excursions were associated with improved oxygenation of the blood, increased carbon dioxide elimination, better acid-base regulation, and greater pulmonary blood flow.—*Artificial pneumoperitoneum in the treatment of pulmonary emphysema, R. H. Furman & J. J. Callaway, Dis. of Chest, September, 1950, 18: 232.—(E. A. Rouff)*

Mediastinal Emphysema.—Dyspnea and cyanosis should arouse suspicion of the presence of mediastinal emphysema in any case

of acute pulmonary infection in the newborn, after operative trauma to the chest in patients with asthma, and in cases of spontaneous chest pain. Postero-anterior roentgenograms may demonstrate one or both mediastinal pleural reflections or may reveal a globular radiolucency superimposed upon the cardiac shadow. It is the lateral projection which in the majority of cases is the most revealing in outlining mediastinal collections of air. A review of 50 cases of mediastinal emphysema emphasized the following points: (*1*) the relationship of pneumomediastinum to pneumothorax and subcutaneous emphysema, (*2*) the value of roentgen examination of the chest before tracheotomy to preclude the possibility of mediastinal emphysema as the cause of extreme dyspnea and cyanosis, and (*3*) the importance of early roentgenographic diagnosis in order to prevent the development of so-called "malignant" penumomediastinum which may be fatal.—*Mediastinal emphysema, J. A. Evans & T. R. Smalldon, Am. J. Roentgenol., September, 1950, 64: 376.*—(*T. H. Noehren*)

Carotid Body Tumors.—A survey of the literature revealed 223 cases of carotid body tumors and to these are added 5 additional cases. The average age at which the tumor is first noted is 34 years, the youngest reported patient being six months and the oldest 76 years of age. There is equal incidence in males and females but malignant tumors are more than twice as common in men as in women. The duration of symptoms averaged seven years and is an index to the very slow growth of these tumors. This is not always true, however, since verified cases are reported with symptoms of a few weeks' to three months' duration. The tumors are usually single but occasional multiple sites of origin are found, presumably representing origin from other branchial glomus bodies. Malignancy occurs in approximately 12 per cent of the tumors, and blood-borne metastases as well as direct extension are reported. The diagnosis is made by the location, consistency and histology of the mass. Commonly, these tumors are situated below the angle of the jaw in the carotid bifurcation and they may present a palpable artery, the external carotid, anterior to their mass. Occasionally the 2 divisions of the common carotid are felt embracing the tumor, and this is diagnostic. Some tumors are hard and are then easily distinguished from branchial cysts. Soft carotid body tumors may be distinguished by the presence of pulsation which disappears with compression of the common carotid on that side. Carotid sinus syncope is not commonly associated with these tumors. Biopsy should confirm the diagnosis and is best made under general anesthesia with full preparation for control of hemorrhage. Histologically the tumor cells are polygonal or spindle shaped, tending to aggregate in clumps suggesting glands; fibrous trabeculae containing many blood vessels intersect the stroma. Treatment is surgical and is undertaken after a preliminary partial ligation of the common carotid to allow increase in the collateral circulation to the brain. Dissection removal is attempted, sparing the carotid vessels. These may be sacrificed if necessary but the operative mortality is raised from 6.5 to 29 per cent thereby. Radiation therapy is reserved for grossly inoperable lesions or for patients who refuse operation.—*The natural history of carotid body tumours and their diagnosis and treatment, R. S. Monro, Brit. J. Surg., April, 1950, 37: 445.*—(*M. G. Carter*)

Aberrant Carotid Body Tumor.—In the human embryo the principal cells of the carotid body arise as a thickening of the media of the internal carotid artery immediately above the bifurcation, that is, from the part of the vessel which represents the commencement of the third branchial arch artery. Carotid body-like tissues are found embryologically in relation to other branchial arches and in the adult may be found as paired organs in relation to the aortic arch, the innominate artery and the pulmonary arteries. The physiologic and morphologic homology of these glomus bodies with the carotid bodies has been established. The occurrence of tumors similar to carotid body tumors is to be anticipated in these aorticopulmonary glomera.

One such tumor occurred in a 22-year-old man who in 1942 had a deeply fixed mass in the left side of the neck; on biopsy the mass showed the spindle-shaped and polygonal cells characteristic of a carotid body tumor. In 1946 there was mottling of the lung radiating from the hili, a calcified nodule in the liver presumed to be a metastasis, and calcification of some of the glands in the root of the neck. No change followed 2 courses of radiation therapy. This is clinically and morphologically similar to known tumors of the carotid body in that it occurred in a young male, has grown slowly, is locally invasive, and has demonstrated the ability to metastasize. A low-grade bronchial or thymic carcinoma might simulate this lesion. However, the presence of a low-grade malignancy of the mediastinum with the histology characteristic of a carotid body tumor is most satisfactorily diagnosed as a tumor of one of the mediastinal homologues of the carotid body, an aortic or pulmonary glomus. This is the first tumor of the aortic and pulmonary glomera to be recorded in man. The patient was alive at the time of the report.—*The morphology of the branchial glomera and their tumors with a report of a case of aortico-pulmonary glomus tumor, R. S. Monro, Brit. J. Surg., July, 1950, 38: 105.—(M. G. Carter)*

Resection in Pulmonary Aspergillosis.—A 48-year-old man gave a history of cough and repeated severe hemoptyses for eighteen months. Chest roentgenograms revealed an area of infiltration in the left clavicular region with a small peripheral cavity. The patient had been hospitalized for one year with the clinical diagnosis of tuberculosis but no tubercle bacilli were demonstrated in the sputum. Numerous examinations for fungi were also negative. Severe bleeding continued until the diseased anterior segment of the left upper lobe was removed. Pathologic examination revealed many conidiophores and septate mycelia characteristic of aspergillosis. No tuberculosis was present. The patient has remained well since operation. No other cases of surgery for pulmonary aspergillosis were found in the literature.—*Segmental resection of the lung for aspergillosis, L. A. Hochberg, E. H. Griffin, & A. D. Bicunas, Am. J. Surg., September, 1950, 53: 364.—(M. G. Carter)*

Pulmonary Abscess.—Of a series of lung abscesses with pleural complications treated by medical means only, it was found that 20 of 34 patients were cured, 5 were improved, 7 resisted medical treatment, and 2 died. The principles employed were those of adequate antibiotic treatment, both parenterally and directly into the lesion, and general symptomatic treatment. Direct instillation of antibiotic into the lesion was effected through the bronchoscope and by bronchial catheter. Bronchoscopic drainage was provided when necessary. When the pleura was implicated, large intrapleural doses of appropriate antibiotics were given. When the lung abscess was located peripherally and endoscopic drainage was impossible, a transpleural approach was used for evacuation and instillation of the antibiotic. Otherwise the transpleural approach was used only if the abscess had ruptured spontaneously into the pleural space. Surgical therapy, preferably excision, is advised if medical treatment produces no further improvement after two or three months' therapy and if a residual cavity can be demonstrated.—*Le traitement médical des abces pulmonaires et de leurs complications pleurales; Importance d'une thérapeutique locale, R. Lapp., Schweiz. med. Wchnschr. June 10, 1950, 80: 604.* (*M. Marcus*)

Middle Lobe Disease.—A total of 19 lobectomies were performed for disease limited to the right middle lobe of the lung, 16 having been done in the past year. Inflammatory disease is often limited to the right middle lobe because of its peculiar anatomic arrangement; the lymph nodes are so arranged about the origin of its bronchus that moderate enlargement of them will cause complete bronchial occlusion. The immediate result is a swollen, dense middle lobe often with early abscess formation. If the acute process subsides and the bronchus reopens, bronchiectasis may

be present. Of the 19 patients, 14 gave a history of an acute onset; all 10 with bronchiectasis had a chronic productive cough; the 6 persons with abscesses initially had acute pneumonic processes; 3 with tuberculosis of the middle lobe also had had abrupt onsets. The most striking finding in this small group was the relatively normal appearance of the frontal roentgenograms of those patients with bronchiectasis; increased bronchovascular marking was the usual report.—*Middle lobe disease, J. R. Bryant & J. S. Harter, Dis. of Chest, September, 1950, 18: 250.*—(*E. A. Rouff*)

Thoracotomy for Solid Pulmonary Infiltrates.—Since 1942, the authors have been performing exploratory thoracotomy for patients whose roentgenograms showed solid, round, sharply demarcated shadows. These patients were free of symptoms and over thirty-five years of age. Extensive preoperative studies were not revealing. The postoperative diagnoses were: pulmonary carcinoma, 4 cases; cyst of the lung, 4; hamartoma, 5; dermoid cyst and intercostal neuroma, 3 each; tuberculoma and diaphragmatic hernia, 2 each; and fibrosarcoma, bronchial adenoma, chronic pulmonary abscess, simple mediastinal cyst, gastric cyst, pulmonary hemangioma, pulmonary hemangiofibroma and aneurysm of the aorta, one each. The prognosis in the 4 cases of carcinoma was certainly improved by surgery. Many of the other conditions, if diagnosed, would have required surgery anyway. The only operative mortality was in the case of aortic aneurysm.—*Diagnostic thoracotomy for solid pulmonary infiltrates, E. Husfeldt & C. V. Carlsen, Thorax, September, 1950, 5: 229.*—(*A. G. Cohen*)

Pharyngeal Diverticulum.—Of 28 patients, ranging in age from two to ninety-two years, with pharyngeal diverticulums, 21 were subjected to surgery. The oldest patient on whom operation was performed was seventy-seven years of age. In the entire surgical group there was only one death, this being due to carcinomatous degeneration of the pharyngeal pouch. There were no postoperative infections or fistulas. It is recommended that all patients with symptoms from a pharyngeal diverticulum be subjected to operation. In the present series, 6 pharyngeal pouches occurred in one family and 2 in another. This, together with the presence of the pouch in a two-year-old child, suggests that a congenital factor may be partially responsible for their origin.—*Pharyngeal diverticulum, T. Dunhill, Brit. J. Surg., April, 1950, 37: 404.*—(*M. G. Carter*)

Alveolar Cell Tumors.—Alveolar cell tumor is a relatively rare condition. It will probably be encountered more frequently because of the present willingness of thoracic surgeons to explore lesions in the lung for which a definite preoperative diagnosis cannot be made. The condition is progressive and ultimately will cause the death of the patient by suffocation or by involvement of distant organs. A series of 12 cases is presented. All of the patients complained of cough but in only 8 cases was sputum produced. In 3 instances the sputum was described as being clear or white, profuse and frothy; in 2 instances the sputum was frankly purulent. Less common symptoms were fever, pain, fatigue, hemoptysis, weakness, and loss of weight. From a study of the 12 cases in this series, it would seem that the earliest form of involvement by alveolar cell tumor is a small, poorly defined area of consolidation similar to the pneumonitis seen following bronchial obstruction or in conjunction with atypical pneumonia. As the disease progresses, it may extend until the entire lobe is involved. Other centers of involvement may then become apparent in the same lobe, in the same lung, or in the opposite lung. There is nothing in the appearance of the roentgenograms in these 12 cases which allowed a definite diagnosis of alveolar cell carcinoma to be made. In the earliest stages the lesion may be confused with pulmonary abscess, with bronchiectasis, or with chronic pneumonitis secondary to bronchial obstruction. The most valuable single aid in diagnosis is the cytologic examination of sputum or bronchial secretions. Surgery offers the only

effective treatment which is known at the present time. Excision is indicated whenever the lesion is localized to one lung or one lobe of the lung.—*Alveolar cell tumors of the lung, C. A. Good, J. R. McDonald, L. T. Clagett, & E. R. Griffith, Am. J. Roentgenol., July, 1950 64: 1.*—(*T. H. Noehren*)

Bronchogenic Carcinoma.—A review of 210 patients with bronchogenic carcinoma seen in the past three years shows a small salvage rate. Fifty per cent of the cases were obviously inoperable when first seen; only half of the remainder were suitable for resection and in some of these only palliative surgery could be accomplished. There were 5 deaths in 72 resections, a mortality rate of 6 per cent. It is doubtful whether this rate can be reduced appreciably in view of the advanced age of most of these patients and the technical difficulties encountered. There was an average delay of five months between the first symptoms and the first visit to a physician and, more importantly, a delay of six months before the proper diagnosis was made. It is estimated that for each month's delay the patient's chances of survival decrease by 25 per cent. The delay in diagnosis is the most important factor and usually is due to one or more incorrect diagnoses, chiefly those of asthma, bronchitis, unresolved pneumonia, virus pneumonia, tuberculosis, and fungus disease. The history and roentgenographic changes are most important in making the proper diagnosis. Early characteristic symptoms are wheeze, cough, and blood-streaked sputum. Localized areas of emphysema or atelectasis with or without circumscribed lesions should make carcinoma the first possibility. Bronchoscopy is important but a negative examination does not preclude the presence of a tumor. Cellular examination of sputum or bronchoscopic lavage specimens is to be trusted only in experienced hands and a negative report cannot preclude a tumor. Exploratory thoracotomy has practically no more surgical risk than an exploratory laparotomy and should be resorted to much more frequently.—*Early detection of bronchogenic carcinoma, R. R. Shaw, Dis. of Chest, September, 1950, 18: 185.*—(*E. A. Rouff*)

Dumbbell Ganglioneuromata—A three-year-old child developed progressive weakness of the legs and trunk, and roentgenograms showed a calcified tumor in the right thoracic apex lying in the posterior mediastinum. A paravertebral mass was also palpable at this level but no bony erosion was present. At laminectomy from D3 to D5, an extrathecal tumor, largely anterior, was removed. This was in continuity with the dorsal intramuscular mass as well as with the intrathoracic mass through an intervertebral neural foramen. Five months later the intrathoracic tumor was removed. Pathologically, the lesion showed ganglion cells, calcium, axis cylinders, and collagen fibers. The patient was well five years after the operation. Seven other ganglioneuromata with "dumbbell" characteristics have been reported, occurring most often between the ages of two to five years. They commonly extend between the ribs to produce paravertebral masses, as well as into the neural foramina to give symptoms of cord compression. The paravertebral or extraspinous component appears more common in the upper thoracic region and must be differentiated from a paravertebral tuberculous abscess. The intrathoracic tumor may also simulate tuberculosis. Dumbbell tumors with extraspinous components may be found in the neck and abdomen but these are always neurofibromata. Ganglioneuromata show no medullated nerve fibers and have no developmental association with the spinal nerves. They probably arise before or during the migration of the sympathetic system laterally from the neural crest, and the dumbbell shape probably results from the formation of the vertebral column around the tumor rather than from prolongation of tumor through a foramen. This early development explains the age incidence and the almost constant association of scoliosis with these lesions.—*Dumbbell ganglioneuromata, C. P. Sames, Brit. J. Surg., April, 1950, 37: 467.*—(*M. G. Carter*)

Adenocarcinoma of Proximal Esophagus.—The majority of esophageal carcinomas are epidermoid as nearly all of the esophagus is lined by stratified squamous epithelium. There are always some submucosal mucus-secreting glands, and often superficial glands resembling gastric glands may be found at both the upper and lower ends of the esophagus. Adenocarcinoma is known to arise in the lower end of the esophagus but no authentic case could be found arising in the upper end. A 64-year-old man developed dysphagia and a biopsy from an esophageal lesion 3 cm. below the cricopharyngeus was reported as a benign adenoma. Resection was performed and the specimen revealed a small patch of columnar epithelium with the structure of pyloric glands. Malignant glands spread from the base of this patch, invading the submucosa and muscularis. The patient was alive and well more than one year following operation.—*Adenocarcinoma of the upper end of the esophagus arising from ectopic gastric epithelium, A. Carrie, Brit. J. Surg., April, 1950, 37: 474.*—(*M. G. Carter*)

Hemothorax.—Hemothorax complicated chest injuries in 171 patients. The cases were divided into three groups: (*1*) small hemothorax, if less than 300 cc. of blood were present, as judged by quantity of fluid aspirated and by roentgenogram; (*2*) moderate hemothorax, if 300 to 800 cc. of fluid were present; and (*3*) large hemothorax if more than 800 cc. of fluid were present. Those patients from whom blood was removed within 72 hours after injury and the chest kept "dry" by frequent thoracentesis were classified as having had sufficient aspirations. Those patients in whom blood was allowed to accumulate or who were not aspirated within 72 hours were said not to have had sufficient aspirations. This division created 2 groups of patients of almost equal numbers. There was no significant difference in the duration of fever or days of hospital stay among patients in the small hemothorax group. In the moderate hemothorax group, those having sufficient aspirations averaged 2.1 days of fever and 5.2 hospital days; those without sufficient aspirations averaged 8.6 days of fever and 18.9 hospital days. In the group with large hemothoraces, those patients with sufficient aspirations averaged 5.5 days of fever and 11.8 hospital days; those without sufficient aspirations averaged 14.2 days of fever and 24.2 hospital days. Decortication was required in 2 per cent of the patients who were adequately aspirated and in 5 per cent of those who were not. The total mortality rate was 15.7 per cent. The mortality of those living more than 24 hours was 4.9 per cent. It is concluded that early repeated aspiration of blood without air replacement is the correct treatment for traumatic hemothorax. This confirms the experiences reported during World War II.—*Treatment of hemothorax, E.B. Hay & J. K. Webb, Am. J. Surg., August, 1950, 70: 240.*—(*M. G. Carter*)

Civilian Chest Wounds.—Penetrating wounds of the chest in civilians usually are due to knives or small caliber bullets and are not open chest wounds. They are quite different from the massive traumatic lacerations reported during World War II where immediate thoracotomy was sometimes necessary. Conservatism is necessary in the treatment of these closed penetrating wounds. This consists of minor debridement and suture of the external wound, parenteral penicillin, 100,000 units every three hours, oxygen inhalation for respiratory distress and aspiration without air replacement for large bloody effusions. Transfusions of whole blood and plasma are used for shock; ligation of bleeding vessels rarely is needed. Tetanus toxoid or antitoxin is used. Fibrothorax, empyema, severe hemorrhage, pneumonitis, and lung abscess may occur but are rarely seen with the treatment outlined.—*Penetrating wounds of the chest, W. E. Walsh, J. G. Stubenbord, & R. W. Tause, Am. J. Surg., August, 1950, 70: 176.*—(*M. G. Carter*)

Bronchial Subdivision in Bronchiectasis.—Preliminary observations of bronchograms and resection specimens in cases of bronchiectasis indicated a reduction in the number of subdivisions of the bronchi between the hilus

and the periphery of the lung. This question was investigated more thoroughly in 45 cases and 3 normal controls. The posterior basal branch of either lower lobe bronchus was selected. The number of its subdivisions was determined both from the bronchograms and from gross and microscopic study of the resection specimens. The average number of subdivisions in the normal lung was 20. The cases of bronchiectasis were divided into 3 groups: (*1*) Cylindrical: No reduction in the number of bronchi was found although fewer were seen in the bronchogram. Failure of a bronchus to fill in the bronchogram was often due to a mucous plug. (*2*) Varicose: The number of bronchi was reduced, both in the bronchograms and specimens. In many cases, larger bronchi persisted as discrete bands beyond the point at which the bronchial lumen was obliterated by fibrous tissue. (*3*) Saccular: This showed the least subdivisions of any of the groups.—*Reduction in bronchial subdivision in bronchiectasis.—L. M. Reid, Thorax, September, 1950, 5: 233.*—(*A. G. Cohen*)

Bronchial Anastomosis.—The left main stem bronchus was accidentally severed during the course of a left lower lobectomy in a 20-year-old man with left lower lobe bronchiectasis. After division of the vessels to the left lower lobe by dissection technique, the clamp on the lower lobe bronchus was inadvertently placed on the main stem bronchus which was divided. The error was recognized, the lower lobe was removed, and that bronchus closed. An end-to-end anastomosis of the main stem was then accomplished with an interrupted suture reinforced with an intercostal muscle graft. The patient recovered uneventfully and was well five months postoperatively. Repeated bronchograms taken three and one-half months postoperatively showed no gross stenosis at the site of anastomosis although an expiratory ronchus was detectable over the left upper lobe.—*Accidental section and successful resuture of a bronchus, J. R. Belcher, Brit. J. Surg., July, 1950, 38: 121.*—(*M. G. Carter*)

Re-expansion after Resection.—The practice of dissecting each element of the pulmonary pedicle has resulted in a marked reduction in mortality and morbidity following pulmonary resections. The problem of obliterating the remaining dead space and at the same time conserving as much pulmonary function as possible has remained only partially solved. Segmental resection, when feasible, is one of the answers. It has been found that the incidence of postoperative complications is directly proportionate to the rate of failure of the operated lung to re-expand. Important points in obtaining complete re-expansion as rapidly as possible are: (*1*) division of all adhesions between parietal and visceral pleurae as well as of interlobar adhesions. (In lower lobectomy the upper lobe should be freed on the costal and mediastinal surfaces, and in upper lobectomy the lower lobe has to be freed from all diaphragmatic attachments); (*2*) severing of the normal attachments such as the triangular ligament to improve mobility of the remaining lung; (*3*) decortication of the remaining lung whenever indicated; (*4*) segmental resection without the use of crushing forceps or sutures, if possible. If resection has been done for tuberculosis, partial thoracoplasty in one stage is recommended to prevent emphysema by overdistention of remaining lung tissue. If the patient's condition permits, this is to be done at the time of resection. If not, no more than three weeks are permitted to elapse between the two operations.—*Le rôle de la réexpansion pulmonaire après résection partielle du poumon, R. H. Overholt & A. P. Half, Schweiz. med. Wchnschr., August 19, 1950, 80: 852.*—(*H. Marcus*)

Gas Exchange During Thoracotomy.—A clinical study of respiratory gas exchange has been made during 53 operations involving open thoracotomy. Curare was give after the thorax was opened, and pulmonary ventilation was maintained by mechanical insufflation. Analyses were made on arterial blood samples taken before, during, and after the procedure. Satisfactory oxygenation was present during the operative period but it was

below normal before and after surgery. There was a tendency towards the development of a respiratory but not a metabolic acidosis during the course of the operations. This was most notable during the pneumonectomies (13 cases), less marked during lobectomies (9 cases), and least obvious in a group of miscellaneous operations. The acidosis is the result of inadequate pulmonary ventilation.—*A clinical study of respiratory exchange during prolonged operations with an open thorax, J. H. Gibbon, Jr., F. F. Allbritten, Jr., J. W. Stayman, Jr., & J. M. Judd, Ann. Surg., October, 1950, 132: 611.—(W. H. Oatway, Jr.)*

Arteriovenous Aneurysms.—A clinicopathologic correlation of pulmonary arteriovenous aneurysm was not made until twelve years ago, and surgery to correct it was not performed until eight years ago. Approximately 50 cases have been reported, and many of them were treated surgically. The differential diagnosis is becoming clearer as are, the clinical, laboratory, and roentgenographic findings. The lesions frequently are multiple. Heredity factors seem to be important and hereditary hemorrhagic telangiectasia commonly is present. Of 4 cases described, resection was attempted successfully in 3. The aneurysms were demonstrated in all 3 resected lobes by bronchovascular injections of colored vinylite plastic. The sacs were close to the pleura, the vessels of more than one bronchopulmonary segment were usually involved, and each aneurysm was formed by more than one artery and vein.—*Pulmonary arteriovenous aneurysm, G. E. Lindskog, A. Liebow, H. Kausel, & A. Jansen, Ann. Surg., October, 1950, 132: 591.—(W. H. Oatway, Jr.)*

Antiocardiography in Lung Cancer.—In general, benign tumors tend to spread or dislocate vessels rather than to occlude them, whereas malignant tumors cause irregular alterations in the contour of vascular lumina, frequently producing complete stenosis of major pulmonary arteries. Experienced interpreters frequently can distinguish by the use of angiocardiography between the vascular distortion of circumscribed masses and the effects of malignant, infiltrative processes. This procedure is of special value to the thoracic surgeon in that it often indicates the anatomical extent of the lesion as no other preoperative examination can. This enables him to plan the most suitable method of approach, informing him regarding the otherwise hidden structures behind the tumor he plans to attack. In a series of 53 cases, an angiocardiographic diagnosis of cancer of the lung was made in 34 patients. A diagnosis of tumor, not specifically primary in the lung, was made in 4 additional cases, while the diagnostic findings were considered inconclusive in the remaining 15 instances. It is emphasized that no patient should be denied exploratory surgery on the basis of angiocardiographic changes alone since non-neoplastic conditions may simulate the malignant changes.—*Lung cancer operability: Angiocardiographic study of fifty-three consecutive proved cases of lung cancer, C. T. Dotter, I. Steinberg, & C. W. Holman, Am. J. Roentgenol., August, 1950, 64: 222.—(T. H. Noehren)*

Treatment of Asthma.—Asthamatic patients were divided into 3 groups: (*1*) Allergic asthma was diagnoced in patients who were demonstrably sensitive to known allergens, whose normal vital capacity was restored by vaponefrin during acute attacks, and whose history and chest roentgenograms failed to reveal recurrent or chronic respiratory infections. (*2*) Infectious asthma was considered to be present in patients who had findings of chronic bronchitis, many of whom had had recurrent attacks of pneumonia or roentgenographic evidence of bronchiectasis, and who had a reduced vital capacity not restored to normal by vaponefrin, and who had no evidence of hypersensitivity. (*3*) Mixed allergic and infectious asthma was diagnosed in patients with the positive findings of both the preceding groups. Oral Neo-Antergan relieved 12 of 14 patients with allergic asthma. Antibiotic agents, chiefly penicillin by the oral, intramuscular, or inhalation route, relieved 37 of 48 patients with infectious asthma.

Antibiotic agents, later accompanied by Neo-Antergan, were effective in 27 of 39 patients with mixed allergic and infectious asthma. Antibiotic therapy was most effective in early bronchopulmonary infections and in the less severe cases. Bronchiectasis disappeared partially or completely in 4 young patients. Neo-Antergan increased the respiratory distress in patients with infectious bronchorrhea, presumably because of its atropine-like and sedative actions; 10 per cent of the treated patients complained of drowsiness. For this reason, it is recommended that antibiotic therapy be used to control the infectious component before the allergic condition is treated in mixed asthma. Severe skin reactions to penicillin were observed in less than one per cent of allergic and nonallergic patients.—*Combined antihistaminic-antibiotic therapy in mixed allergic and infectious respiratory conditions, W. Finke, Am. Practitioner, October, 1950, 1:* 1017.—(*L. B. Hobson*)

ANTIMICROBIAL THERAPY

Streptomycin for Tuberculous Meningitis.—A total of 450 cases of tuberculous meningitis has been treated in various hospitals. Bacteriologic proof was obtained in 369. There were 104 survivors. Better results were obtained in cases diagnosed early. Of the survivors, 89 per cent are clinically fit and well and 31 per cent have normal cerebrospinal fluids. Intramuscular streptomycin alone has not been successful. Results were proportionate to the duration of intrathecal streptomycin therapy. The optimum duration of intrathecal therapy beyond the seventy-fifth day is not known. Patients with miliary tuberculosis should have examinations of the cerebrospinal fluid periodically even during streptomycin therapy; complicating meningitis has appeared as late as the seventh month. Prophylactic intrathecal streptomycin is not effective. The standards for normal cerebrospinal fluid are: not more than 4 cells per cm., protein less than 40 mg. per cent, and sugar more than 45 mg. per cent. There were no relapses in patients who achieved this standard with treatment.—*Streptomycin in the treatment of tuberculous meningitis, Ministry of Health, Tubercle, September, 1950, 31: 214.*—(*A. G. Cohen*)

Streptomycin for Tuberculous Meningitis.—A series of 27 patients with tuberculous meningitis were studied to determine the effect of streptomycin on the course of the disease. The general sequence of events tended to follow a rather definite pattern. One-third of the patients manifested no improvement whatsoever and died within a month of the institution of treatment. The remaining patients demonstrated an unequivocally favorable response to treatment as judged by symptomatic improvement, the return of the cerebrospinal fluid glucose content to normal, and disappearance of organisms from the cerebrospinal fluid. Increased cells and protein and decreased chlorides in the spinal fluid often persisted for many months. At the beginning of the third month of treatment, almost one-half of the surviving patients relapsed in spite of continued therapy. A reduction in cerebrospinal fluid glucose content usually heralded this unfortunate event. This decline was often temporarily arrested by the reinstitution of frequent intrathecal injections of streptomycin, but in this series only one such patient ultimately survived. Three patients completed the prescribed five-month period of therapy, and in all 3 the meningitis relapsed or recurred several months later. At the time of reporting, 6 of the 27 patients were alive from 18 to 31 months after the institution of treatment. Of the survivors, two continued with moderate residual neurologic damage and the third had had grand-mal seizures but was otherwise entirely normal. Most patients exhibiting a favorable response to treatment received more than 60 mg. of streptomycin per kg. of body weight per day intramuscularly and more than 2.0 mg. per kg. per day intrathecally. Toxic reactions to streptomycin are common at high dosage but are a justifiable risk. Prognosis of tuberculous meningitis must still be considered to be very grave.—*The effect of streptomycin on tuberculous meningitis, H. D.*

Brainerd & H. R. Eagle, Ann. Int. Med., August, 1950, 33: 397.—(T. H. Noehren)

Therapy of Tuberculous Meningitis.—Between September, 1947 and March, 1950, 94 bacteriologically proved cases of tuberculous meningitis were treated with streptomycin. Prior to the use of this drug, 297 patients had been treated, all of whom died in coma within two to three weeks. At the beginning of the streptomycin era, it was necessary to develop proper dosage schemes by trial and error. Therefore, the earlier results were not as good as later results. There were 19 cures (20 per cent). Children under two years of age rarely survived. Of 14 patients in this group, 13 are dead. The best results were obtained in the two- to four-year-old group, with 5 recoveries in 17. In the five- to nine-year-old group, there were 5 recoveries in 20; ten to fourteen years, one in 6; fifteen years and over, 7 in 37. Two of 5 cases gave a history of prolonged contact with open tuberculosis within three months of the onset. There were other tuberculous lesions in many of the patients. All patients received 0.5 gm. of streptomycin intramuscularly twice a day for at least six months. Intrathecally, 100 mg. of the drug were given in a few cc. of saline daily for a least six weeks and, if necessary, for three to four months. After each seven days, a three-day rest period was given to avoid a sore back. If the patient's condition was good at the end of six weeks, intrathecal injections were given every other day and later every third day. Streptomycin bichloride was the preferred preparation. Recently streptokinase has been tried with no special benefit. Four of the 19 recovered patients are deaf.—*The treatment of tuberculous meningitis, C. J. McSweeney, Tubercle, September, 1950, 31: 210.—(A. G Cohen)*

PAS for Draining Empyema.—The effect of oral *p*-aminosalicylic acid (PAS) therapy and local PAS packs was studied in a group of 22 patients, all of whom had tuberculous empyemas with secondary infections. All had thoracotomies; 12 had had thoracoplasty; 2, pneumonectomy; one, a lobectomy; 4, unroofing operations; one, a decortication; and one, had had a cavernostomy. Eleven then received the sodium salt of PAS, 3 gm. four times per day, orally for 120 days; the other 11 were given a placebo mixture. After 60 days of therapy equal numbers then were treated twice daily with sodium PAS in 5 per cent packs for the remaining 60 days. Saline packs were used in several other cases in the same period. It was not believed that the PAS therapy produced any significant improvement in the treated cases but that the local packs of sodium PAS caused some thinning and lessening of the drainage and produced a cleaner wound.—*The use of PAS in the treatment of draining tuberculous empyemata, M. R. Lichenstein & Alfano, Dis. of Chest, August, 1950, 18: 93.—(E. A. Rouff)*

Reactions to Dihydrostreptomycin.—In 9 of 10 patients with neurotoxic reactions to dihydrostreptomycin, the reactions probably were due to the presence of too great a concentration of the drug in the blood plasma rather than to idiosyncrasy to the drug. It seems likely that a maximal daily concentration of more than 60 γ per cc. for several weeks frequently will damage either the vestibular or the auditory system. The high concentrations were attributed to administration of a total daily dose of 3 gm. in 2 cases, to administration of 2 gm. in a single daily injection in 3 cases, to the presence of impaired renal function in 3 cases, and to a combination of 2 of these factors in one case.—*Neurotoxic reaction to dihydrostreptomycin, D. T. Carr, H. A. Brown, C. H. Hogdson, & F. R. Heilman, J.A.M.A., August 5, 1950, 143: 1223.—(H. Abeles)*

Atypical Pneumonia.—Fourteen patients acutely ill with primary atypical pneumonia were treated with aureomycin; 12 patients received 250 mg. at six-hour intervals and 2 were treated at four-hour intervals. There was prompt and adequate response to this treatment by all patients. No relapses were observed. Gastrointestinal complications were

minimal.—*Dosage of aureomycin in primary atypical pneumonia, W. A. Blodgett, J. H. Keating, & G. J. Caffin, J.A.M.A., July 8, 1950, 143: 878.*—(*H. Abeles*)

LABORATORY STUDIES

Culture of Tubercle Bacilli.—The relative efficiency of Dorset egg, Middlebrook agar, and Petroff egg culture media was tested in the examination for tubercle bacilli of sputum and gastric washings collected in a chest clinic. Two samples of each specimen were digested, one with sodium hydroxide, the other with trisodium phosphate. The sediments obtained by centrifuging were neutralized and equal amounts were inoculated on each medium. In all, 69 sputum and 5 gastric specimens were treated with trisodium phosphate and 87 sputum and 7 gastric samples, with sodium hydroxide. Approximately twice as many positive cultures were found on Middlebrook's medium as on either of the others, irrespective of the method of concentration; the sodium hydroxide method always gave more positive results. Contamination was more frequent with trisodium phosphate than with sodium hydroxide and was least on the Middlebrook medium, presumably because of the presence of penicillin. A shorter incubation time was required with the Middlebrook medium, increasing the chances for error due to acid-fast saprophytes; the virulence of the cultures could be determined by guinea pig inoculation. The Middlebrook agar medium had the advantage of quicker preparation, requiring only one and one-half days for compounding, sterilising, tubing, and waxing. Egg media required four days for preparation. The Middlebrook medium appears to have greater efficacy than either the Petroff or Dorset medium as a diagnostic aid.—*An evaluation of certain culture media for tubercle bacilli, B. B. Byham, Am. J. Clin. Path., July, 1950, 20: 678.*—(*J. S. Woolley*)

Media for M. Tuberculosis.—The authors' media consist of an agar vase to which is added, after cooling to 55°C., egg-yolk enrichment. The keeping qualities are good. The agar base contains beef extract, casein hydrolysate, potato starch, asparagine, ferric ammonium citrate, magnesium sulfate, and 1.5 per cent agar with dipotassium phosphate buffer. There are 2 types of egg-yolk enrichment, one of which is added to each liter of the agar base. "A" contains 10 egg yolks plus sodium chloride, glycerin, dextrose, and malachite green. "B" contains 5 egg yolks, sodium oleate, glycerin, and the dye. Sputum and gastric concentrates were inoculated on these 2 media and on Petragnani's and Loewenstein's media. The authors' media yielded more positive cultures; growth appeared earlier and was more profuse. Cultures of 2,275 sputum and gastric concentrates showed 15.2 per cent positives on the modified Loewenstein's medium, 17 per cent on the authors' agar "A", and 16 per cent on agar "B".—*A new medium for bacteriologic diagnosis of tuberculosis, L. R. Peizer & C. Schecter, Am. J. Clin. Path., July, 1950, 20: 682.*—(*J. S. Woolley*)

Isolation of Tubercle Bacilli.—The authors have sought the best technique for the isolation of tubercle bacilli from sputum prior to the study of their resistance to streptomycin. Trisodium phosphate provides better results than sulfuric acid or potash in the preliminary elimination of other microorganisms. Sulfuric acid is a powerful disinfectant in regard to the other organisms but slows or prevents the growth of tubercle bacilli. The preferred method consists in making an emulsion of sputum with five or six times its volume of 10 per cent trisodium phosphate; Corper and Sterner employ equal parts. After thorough agitation the mixture is left for twenty-four hours at 37°C., centrifuged, the sediment washed (preferably with Sorensen's solution, pH 7), and cultured. In considering choice of media, those containing malachite green are preferred to those containing Congo red, especially when many different microbes are known to be present. The Dubos medium is faster but not quite as reliable as Loewenstein's medium. The inoculation of guinea pigs, while the slowest method of isolation, has in some

cases given positive results when the cultures remained negative.—*Au sujet des methodes d'isolement et de culture des bacilles de Koch, C. Gissens-Decavel, Rev. belge path., December, 1949, 19: 309.*—(*A. T. Laird*)

Cortisone in Experimental Tuberculosis.—Cortisone produced a marked exacerbation in experimentally produced tuberculosis in mice. The effect was more readily demonstrable in a chronic type of disease produced by a smaller amount of dried tubercle bacilli. The effect is probably not due to a reduction in sensitivity or to a decrease of fibrous tissue formation.—*Enhancing effect of cortisone on tuberculosis in the mouse, P. D'A. Hart & R. J. W. Rees, Lancet, September 23, 1950, 2: 391.*—(*A. G. Cohen*)

PUBLIC HEALTH AND EPIDEMIOLOGY

BCG.—There is doubtless justification for a BCG vaccination program in areas where it is impossible to employ the usual tuberculosis control measures. It is difficult, however, to recommend the widespread use of BCG in the United States. In spite of the extensive use of BCG, there are gaps in our knowledge of this subject which may be significant. There is little uniformity in the number of viable organisms in the several vaccines now being produced. Little is known concerning the number of viable organisms required in the injected dose and the significance of the nonviable organisms. The life of the vaccine is a matter of conjecture. Tests with dried vaccines have not been encouraging. The evaluation of the tuberculin test, its dosage and its interpretation, affects the comparability of the results reported by different workers. The degree of allergy produced by BCG vaccination varies considerably. There is disagreement on the most efficacious method for administering BCG. The intradermal method seems to be more efficient in producing allergy. The decline in tuberculosis mortality and morbidity in France or Denmark constitutes no evidence that BCG vaccination was effective. The tuberculosis mortality in Iceland declined considerably without the use of BCG. In the Middle West, where tuberculin reactors are known to be less than 10 per cent in the teenage group, vaccination would produce a tuberculin-sensitive population in an area that is approaching the goal of any tuberculosis control program, a population entirely free of infection and disease. On the other hand, vaccination of 'exposed' groups means vaccinating where the least number of persons eligible for vaccination can be found. The most that can be suggested at this time is the use of vaccination in selected groups in which known exposure exists. Mass vaccination programs are warranted only for carefully documented evaluation studies.—*BCG, R. J. Anderson & C. E. Palmer, J.A.M.A., July 22, 1950. 143: 1048.*—(*H. Abeles*)

Tuberculosis in Nurses.—The Central Middlesex Hospital in England is a general hospital which was obliged to admit cases of active tuberculosis. These were placed on separate wards and precautions were taken on behalf of the student nurses. Tuberculin tests were made on admission to training and repeated every three months. The convertors were checked carefully by sedimentation rate and roentgenograms every three months for a year. They were not permitted to work on tuberculosis wards for a year thereafter. Tuberculin-negative nurses were never allowed to work on these wards. The conversion rate during the first year of training was 27.9 per cent. Of the convertors, 10.5 per cent showed symptoms. In the others, the roentgenograms remained normal. It thus was possible to use general hospital beds for acute tuberculosis without endangering the student nurses.—*Nursing and tuberculosis in a general hospital, K. P. Ball, H. Joules, C. H. C. Toussaint, & J. A. Heady, Lancet, July 22, 1950, 2: 121.*—(*A. G. Cohen*)

Reliability of Roentgenographic Surveys.—The reliability of carefully performed roentgenographic surveys is high but there is a significant degree of error which is 13 to 27 per cent in experienced hands and up to 46 per cent with less experienced personnel. The

percentages of variation are based only on the number of positive films overread or underread. When 399 films were read and reread several times by a group of competent radiologists, 16 per cent of inter-individual and 8 per cent of intra-individual disagreements were noted as to presence or absence of a lesion. A series of 1,807 miniature films from a mass survey were read by 3 radiologists and 2 chest specialists. The range of individual variation in reported positives was 32 to 83 cases. The total number of cases called positive was 254. The number finally agreed upon by the entire group of readers as definitely positive was 30. Less thoroughly trained readers missed more positives by a factor of 62 per cent. Dual readings were tested and resulted in detection of 34 per cent of the positive films missed by a single reading.—*On the reliability of roentgen survey procedures, L. H. Garland, Am. J. Roentgenol., July, 1950, 64: 32.*—(*T. H. Noehren*)

Tuberculin-Jelly Test.—The "tuberculin-jelly" test requires no injection, but it is necessary to discover a technique and type of jelly which closely approximate the accuracy and sensitivity of the Mantoux test. Three preparations containing 0.2 per cent PPD, 60 per cent OT, and 85 per cent OT, respectively, were prepared in a tragacanth and glycerin base. Following cleansing with acetone, the skin was gently rubbed with a very fine abrasive flour-paper and the jelly applied to an area approximately 2 cm. long and 2 or 3 mm. wide. The site was then covered by an adhesive plaster which was removed after 48 hours. The test, read 72 to 96 hours after the application of the jelly, was positive if 4 or more vesicles appeared at the site of application. Erythema was ignored. Employing this technique with patients between the ages of five and twenty, it was found that the PPD jelly was approximately equal to an intradermal injection of 0.1 ml. of OT in a dilution of 1:10,000, whereas the 60 per cent OT jelly preparation was equivalent to an intradermal injection of OT 1:1,000. Positive results to both jelly and injection showed a correlation of 92 to 99 per cent. Only 2 patients (0.9 per cent) in this series reacted to an intradermal test without reacting to the jelly test. There was a higher correlation of the intradermal test with the OT jelly than with the PPD jelly, but there was no difference between the 60 per cent and 85 per cent OT preparations. The difference was ascribed to better skin absorption of the OT preparations. The test has value as a screening procedure before proceeding to an intradermal test with OT, 1 to 100.—*Value of tuberculin-jelly test, W. P. Dick, Brit. M. J., July 15, 1950. No. 4671: 141.*—(*E. A. Riley*).

Calcification in Histoplasmosis.—Determination of the frequency of postive skin reactions to histoplasmin was made in the area of Manitoba to evaluate the correlation between skin sensitivity and the incidence of pulmonary calcification in that region. In a group of 440 veterans in Manitoba, many of whom had traveled widely during war service, the incidence of positive skin reactions to 1:100 histoplasmin was 5 per cent. This figure is similar to that reported in Minnesota, immediately south of this region. Calcifications were found in the following ratios to skin tests: histoplasmin and tuberculin negative, 5 per cent; histoplasmin negative and tuberculin positive, 15 per cent; histoplasmin positive and tuberculin negative, 63 per cent; histoplasmin positive and tuberculin positive, 53 per cent.—*Pulmonary calcifications and histoplasmin sensitivity, P. Green, Canad. M. A. J., August, 1950, 63: 143.*—(*T. H. Noehren*)

. . . when oral therapy is not feasible

. . . in severe, fulminating or necrotizing infections

. . . in pre- and postoperative prophylaxis

. . . in peritonitis

CRYSTALLINE

Terramycin

HYDROCHLORIDE

for hospital use only

INTRAVENOUS

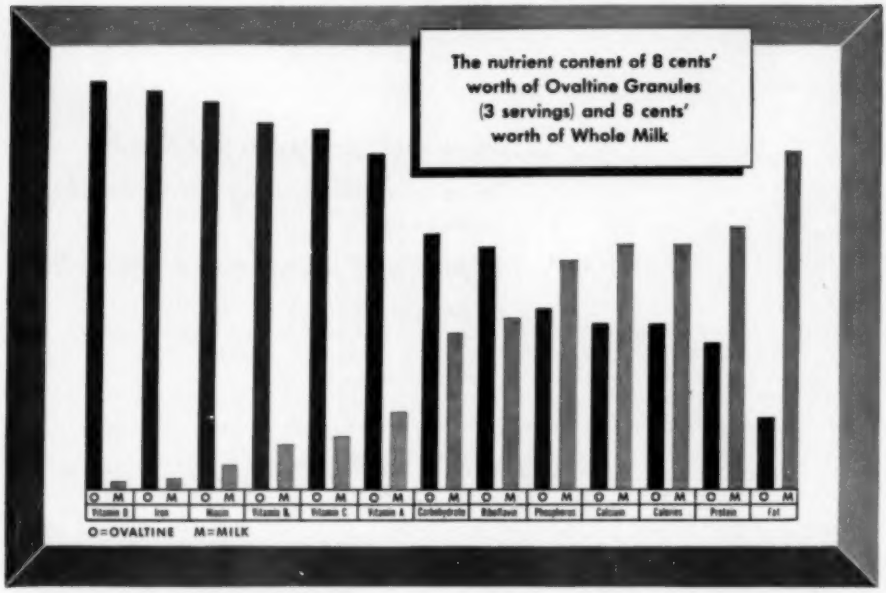
CRYSTALLINE TERRAMYCIN HYDROCHLORIDE FOR INTRAVENOUS INJECTION

affords *rapid* control of infections caused by organisms in the bacterial, rickettsial and certain viral and protozoan groups

Supplied: 10 cc. vials containing 250 mg. of Crystalline Terramycin Hydrochloride with sodium glycinate as a buffer.

20 cc. vials containing 500 mg. of Crystalline Terramycin Hydrochloride with sodium glycinate as a buffer.

Antibiotic Division Pfizer CHAS. PFIZER & CO., INC., *Brooklyn 6, New York*



Note the *Outstanding Economy* of OVALTINE

NUTRIENTS	OVALTINE*	WHOLE MILK**
Vitamin D	400 I.U.	8 I.U.
Iron	12 mg.	0.3 mg.
Niacin	6 mg.	0.4 mg.
Thiamine	0.90 mg.	0.16 mg.
Ascorbic acid	30 mg.	4 mg.
Vitamin A	2025 I.U.	625 I.U.
Carbohydrate	29 Gm.	19 Gm.
Riboflavin	0.75 mg.	0.66 mg.
Phosphorus	255 mg.	363 mg.
Calcium	255 mg.	460 mg.
Calories	160	269
Protein	6.5 Gm.	13.6 Gm.
Fat	2 Gm.	15 Gm.

* 8 cents' worth of Ovaltine (3 servings)
** 8 cents' worth of milk

As the bar chart so vividly indicates, Ovaltine is an exceptionally economical source of many essential nutrients. Using whole milk as the basis for comparison, the chart contrasts the relative amounts of nutrients supplied by 8 cents' worth of Ovaltine granules (3 servings) and by 8 cents' worth of whole milk. In 8 of the 13 nutrients listed, Ovaltine supplies greater amounts, and in the remaining 5, high proportions of the amounts found in milk.

It should be noted that Ovaltine specially enriches milk in those nutrients in which milk is low. Thus Ovaltine is not only economical in use but constitutes with milk an ideal protective supplementary food drink. It finds wide usefulness whenever dietary supplementation becomes necessary, either because of poor appetite, inability to consume a normal diet, or illness which often makes normal eating difficult or impossible.

THE WANDER COMPANY
360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.

"...the only drug we have seen that allays anxiety without clouding consciousness"

J.A.M.A. *140*:872 (June 25) 1949

Tolserol (Squibb *Mephenesin*)

- to alleviate pronounced anxiety and tension
- as an adjunct in the treatment of chronic alcoholics

DOSAGE

In anxiety tension states:

As little as 0.5 Gm., given orally every few hours, has produced a good response. However, for optimum effect, 0.75 Gm. or more is given several times a day.

As an adjunct in the treatment of chronic alcoholics:

As much as 3 Gm. orally every four hours has been found useful in the acute stage. This dosage is reduced when the patient becomes more manageable. (If Tolserol is given too soon after the patient drank alcohol, the toxic effect of the alcohol may be potentiated. For this reason, Tolserol should not be administered until six hours have elapsed since the patient drank alcohol.)

Tablets, 0.5 Gm., 0.25 Gm.; *Capsules*, 0.25 Gm.; *Elixir*, 0.1 Gm. per cc.; *Solution*, 2% (intravenous).

Tolserol ***(Squibb Mephenesin)***

SQUIBB 745 FIFTH AVENUE, NEW YORK 22, NEW YORK
MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

"TOLSEROL" ® REGISTERED TRADEMARK OF E. R. SQUIBB & SONS

Now on the Press

TWELVE-YEAR CUMULATIVE INDEX AMERICAN REVIEW OF TUBERCULOSIS

Every Review subscriber will welcome the news that a new Cumulative Index is now being printed which will afford ready access to the wealth of scientific and clinical data embodied in the 144 issues published between January 1937 and December 1948. The new index provides almost 10,000 cross-references to more than 1,800 papers by some 3,000 authors.

Each of the 1,800 papers is fully indexed by author, title, subject, date of issue and page number. More than 500 subject headings arranged alphabetically assure quick, easy location of any required article.

The Cumulative Index is a paper-covered volume of 200 pages in the same size as the Review itself, adaptable for binding in series with bound volumes of the Review. A price has been established which represents merely production and handling expenses—$2.50 postpaid (25 cents extra for foreign postage).

IMPORTANT NOTE: A few copies of the 1917–1936 Cumulative Index, covering the contents of the American Review of Tuberculosis during its first 20 years of publication, are still available at a reduced price of $1.00. To receive your copy, note your request on the order form.

AMERICAN REVIEW OF TUBERCULOSIS
1790 Broadway, New York 19, N. Y.

Send me _____ copies of the new Cumulative Index for the 12-year period 1937–1948 inclusive. I enclose payment at the rate of $2.50 a copy (25 cents per copy additional foreign postage).

NAME _____

CITY and STATE _____

Use this convenient order form to send your order—TODAY.

ROUTINE CHEST X-RAYS–

easy to take

easy to file

with FAIRCHILD'S

70mm FLUORO-RECORD CUT FILM CAMERA

Many hospitals are making routine chest x-rays as standard procedure on all admissions and "out" patients, and for periodic checkups on all hospital personnel. Not only does this routine procedure aid in the discovery of tuberculosis, but it also indicates signs of other chest ailments.

With its 70mm Fluoro-Record Cut Film Camera, Fairchild offers an inexpensive means of obtaining 2½ x 2½- or 2½ x 3-inch x-ray negatives. Each 6½ x 2 11/16-inch cut film sheet gives two individual x-rays or a stereo pair. This small exposure size simplifies filing in a minimum space – and yet, is large enough for easy interpretation.

The two-exposure cut film holder is accurately positioned for each exposure by either direct manual or remote electrical control.

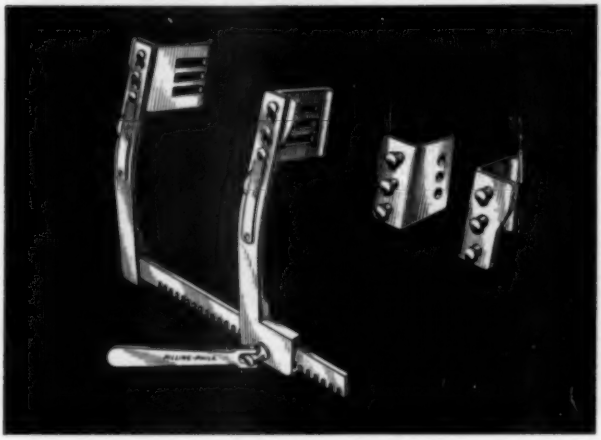
The camera may be adapted for use with many types of existing x-ray equipment or procured with new photo x-ray units of leading manufacturers. See your supplier or write for more data to 88-06 Van Wyck Boulevard, Jamaica 1, N. Y., Dept. 160-11B2.

Fairchild also makes the New Roll Film Cassette for angiographic studies . . . 70mm roll film cameras for mass chest x-rays . . . 70mm cut film and roll film viewers . . . 70mm film processing equipment . . . and the Chamberlain X-Ray Film Identifier.

Fairchild

CAMERA AND INSTRUMENT CORPORATION

Authentic Instruments
FOR THE THORACIC SURGEON



BURFORD MODIFICATION OF THE
FINOCHIETTO RIB SPREADER

Thoracic surgeons look to Pilling for the new and important instruments in their special field. Since 1814, leaders in this field have consulted Pilling and designed instruments to fit their exacting requirements, confident in their knowledge that Pilling craftsmen would create the instruments they desired.

A fine example of Pilling craftsmanship is the Finochietto Rib Spreader, originally designed by Professors Henrique and Ricardo Finochietto of Buenos Aires. Now, the modification of this popular instrument by Thomas H. Burford, M.D., Barnes Hospital, St. Louis, provides even greater versatility. By properly switching the two pairs of interchangeable blades, the instrument can be used as medium or large size, or combinations of one large and one small blade. The shafts are also curved to conform to body curvature, thus keeping the spreader out of the operator's way.

ORDER Instruments direct from

George P. Pilling and Son Company

3451 WALNUT STREET
Philadelphia

SAROT
Bronchial Clamp
Available in pairs—right and left

SAROT
Intra-Thoracic Artery Clamp

SATINSKY
Scissors

SATINSKY
Vena Cava Clamp

A Standing Invitation: When in Philadelphia, visit our modern sales rooms and manufacturing plant. Free parking on our private lot.

INSTRUMENTS BY— Pilling

PILLING FOR PERFECTION in surgical instruments

ALUM ROCK SANATORIUM

SAN JOSE, CALIFORNIA

Telephone Claybourn 8-4921

A non-profit sanatorium for the treatment of Tuberculosis and other diseases of the chest.

Medical Director
Rudred H. Wareing, M.D.
Associate Medical Director
C. Gerald Bjorkenstam, M.D.

Visiting Medical Staff:
Osbert Brown, M.D., San Francisco — H. Corwin Hinshaw, M.D., San Francisco
Gerald L. Grumbine, M.D., Oakland — W. Dale Patterson, M.D., Oakland
J. Lloyd Bostic, M.D., Oakland — Glenray N. Flores, M.D., San Francisco
Ian Crawley, M.D., Oakland — Harold Guyon Tyndale, M.D., Oakland
James Robert Wood, M.D., Oakland

Consulting Pathologist
R. Guyn Roberts, M.D., San Francisco

STAFF AND RESIDENT PHYSICIANS WANTED

STAFF AND RESIDENT PHYSICIAN: Large tuberculosis hospital with surgery, rehabilitation, outpatient services. American graduates eligible for Indiana license considered. Write Superintendent and Medical Director, Healthcare Hospital, 1111 West Darden Road, South Bend, Indiana.

SENIOR RESIDENT PHYSICIAN: Modern Tuberculosis hospital. American training, ultimate New Jersey license required. Salary open. Write Superintendent and Medical Director, Valley View Sanatorium, Paterson, New Jersey.

NATIONAL TUBERCULOSIS ASSOCIATION

Annual Meeting — May 15–18, 1951

Cincinnati, Ohio

The annual meeting of the National Tuberculosis Association will be held in Cincinnati, Ohio, May 15–18, 1951. The Netherland Plaza Hotel will be headquarters.

Some 1500 rooms have been promised by the hotels listed below for the accommodation of those attending the meeting. Arrange to share a double room if possible.

Application for room reservations should be made directly with the hotel of your choice.

Hotel	*Address*	*Single*	*Double*
Netherland Plaza	Carew Tower	$4.00-$10.00	$9.00-$11.00
Sheraton-Gibson	421 Walnut Street	$4.00-$12.00	$7.50-$12.00
Terrace Plaza	15 West Sixth Street	$7.00-$12.00	$10.00-$15.00
Sinton Hotel	4th at Vine Street	$4.00-$10.00	$8.00-$12.00
Fountain Square	420 Vine street	$4.00-$5.50	$8.00-$8.50
Palace Hotel	6th at Vine Street	$2.50-$4.00	$4.00-$7.00
Metropole Hotel	609 Walnut Street	$3.00-$6.00	$6.50-$10.00
Broadway Hotel	4th and Broadway	$3.50	$5.50-$6.50
Alms Hotel	Victory Pkwy. & McMillan	————	$7.50-$15.00

See March issue of NTA Bulletin for preliminary program.

EFFERVESCENT PARASAL* TABLETS

. . . the logical solution to the many problems of P. A. S. administration

In the P.A.S. therapy of tuberculosis, EFFERVESCENT PARASAL TABLETS —newest of Panray's formulations— are fast becoming the preferred dosage form for children and adults. One tablet dropped into water effervesces and dissolves almost instantly, providing 2 grams of active P.A.S. in a pleasantly-flavored, clear solution.

GREATER ACCEPTABILITY to the PATIENT: EFFERVESCENT PARASAL TABLETS are pleasantly mint flavored. They can be taken in water, milk, or fruit juices. And the patient need no longer swallow a huge number of tablets every day. Just 1½ tablets q.i.d. is sufficient to give the average dose of 12 gms. daily.

GREATER CONVENIENCE: Now you need no longer worry about time-consuming filtrations, storage problems, decomposition of solutions, etc. EFFERVESCENT PARASAL TABLETS, bisected for even greater convenience, *always and instantly provide a fresh, fully potent solution.*

GREATER ECONOMY: EFFERVESCENT PARASAL TABLETS eliminate the high costs of extra labor . . . wasted batches . . . refrigeration . . . time-consuming calculations. You simply use tablets as needed. Yet the equivalent cost is no higher than that of other Parasal dosage forms.

MORE ACTIVITY PER TABLET: EFFERVESCENT PARASAL TABLETS have the highest potency of any P.A.S. tablet yet produced. Each tablet contains 2 grams of active Parasal, *4 times as much as any Parasal tablet designed for oral ingestion.*

MORE RAPID ABSORPTION: Since the patient ingests a solution rather than tablets or granules, it is almost certain that the drug will be rapidly and completely absorbed. *Samples and prices on request.*

*Panray's brand of Para Aminosalicylic Acid

THE Panray CORP.

820 CANAL STREET, NEW YORK 13, NEW YORK